Journal of Clinical Lipidology (2019) 13, 287–300

Journal of Clinical Lipidology

Comparative aspects of the care of familial hypercholesterolemia in the "Ten Countries Study"

Jing Pang, PhD, Dick C. Chan, PhD, Miao Hu, PhD, Lauretta A. Muir, PhD, See Kwok, MD, Min-Ji Charng, MD, Christopher M. Florkowski, MD, Peter M. George, MBBS, Jie Lin, MD, Do Doan Loi, MD, A. David Marais, MD, Hapizah M. Nawawi, MD, Lourdes E. Gonzalez-Santos, MD, Ta-Chen Su, MD, Thanh Huong Truong, MD, Raul D. Santos, MD, Handrean Soran, MD, Brian Tomlinson, MD, Shizuya Yamashita, MD, Zanfina Ademi, PhD, Gerald F. Watts, MD, DSc*

School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia (Drs Pang, Chan, and Watts); Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong, SAR (Drs Hu and Tomlinson); Biochemistry and Pathology, Canterbury Health Laboratories, Lipid Clinic, Christchurch Hospital, University of Otago, Christchurch, New Zealand (Drs Muir, Florkowski, and George); University of Manchester, Faculty of Biology, Medicine and Health, Manchester, United Kingdom (Drs Kwok and Soran); Cardiovascular Trials Unit, Clinical Trial Management Office, Manchester Royal Infirmary, Manchester, United Kingdom (Drs Kwok and Soran); Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan (Dr Charng); Faculty of Medicine, School of Medicine, National Yang–Ming University, Taipei, Taiwan (Dr Charng); Department of Atherosclerosis, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing, China (Dr Lin); Department of Cardiology, Hanoi Medical University, Hanoi, Vietnam (Drs Loi and Truong); Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam (Drs Loi and Truong); Division of Chemical Pathology, University of Cape Town Health Science Faculty, South Africa (Dr Marais); Institute of Pathology, Laboratory and Forensic Medicine (I–PPerForM), Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh, Selangor, Malaysia (Dr Nawawi); Department of Cardiology, Section of Preventive Cardiology, UP–Philippine General Hospital, Manila, Philippines (Dr Gonzalez-Santos); Departments of Environmental and Occupational Medicine, Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan (Dr Su); Lipid Clinic Heart Institute (InCor), University of São Paulo Medical School Hospital and Hospital Israelita Albert Einstein, São Paulo, Brazil (Dr Santos); Departments of Cardiovascular Medicine and Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan (Dr Yamashita); Rinku General Medical Center, Osaka, Japan (Dr Yamashita); School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia (Dr Ademi); and Department of Cardiology, Lipid Disorders Clinic, Cardiometabolic Services, Royal Perth Hospital, Perth, Western Australia, Australia (Dr Watts)

* Corresponding author. Department of Cardiology, Lipid Disorders Clinic, Royal Perth Hospital, GPO Box X2213, Perth, WA 6847, Australia.
E-mail address: gerald.watts@uwa.edu.au

Submitted October 29, 2018. Accepted for publication January 21, 2019.

https://doi.org/10.1016/j.jacl.2019.01.009

KEYWORDS:
Familial hypercholesterolemia;
Health care;
Services;
Facilities;
Asia-pacific region;
Southern hemisphere

BACKGROUND: There is a lack of information on the health care of familial hypercholesterolemia (FH).

OBJECTIVE: The objective of this study was to compare the health care of FH in countries of the Asia-Pacific region and Southern Hemisphere.

METHODS: A series of questionnaires were completed by key opinion leaders from selected specialist centers in 12 countries concerning aspects of the care of FH, including screening, diagnosis, risk assessment, treatment, teaching/training, and research; the United Kingdom (UK) was used as the international benchmark.

RESULTS: The estimated percentage of patients diagnosed with the condition was low (overall <3%) in all countries, compared with ~15% in the UK. Underdetection of FH was associated with government expenditure on health care ($\varkappa = 0.667$, $P < .05$). Opportunistic and systematic screening methods, and the Dutch Lipid Clinic Network criteria were most commonly used to detect FH; genetic testing was infrequently used. Noninvasive imaging of coronary calcium and/or carotid plaques was underutilized in risk assessment. Patients with FH were generally not adequately treated, with <30% of patients achieving guideline recommended low-density lipoprotein cholesterol targets on conventional therapies. Treatment gaps included suboptimal availability and use of lipoprotein apheresis and proprotein convertase subtilsin-kexin type 9 inhibitors. A deficit of FH registries, training programs, and publications were identified in less economically developed countries. The demonstration of cost-effectiveness for cascade screening, genetic testing, and specialized treatments were significantly associated with the availability of subsidies from the health care system ($\varkappa = 0.571$–0.800, $P < .05$).

CONCLUSION: We identified important gaps across the continuum of care for FH, particularly in less economically developed countries. Wider implementation of primary and pediatric care, telehealth services, patient support groups, education/training programs, research activities, and health technology assessments are needed to improve the care of patients with FH in these countries.

Introduction

Familial hypercholesterolemia (FH) is a dominantly inherited disorder owing to gene variants in the low-density lipoprotein (LDL) receptor pathway that cause markedly elevated plasma LDL cholesterol concentrations.[1] Untreated FH leads to premature death from coronary artery disease (CAD) due to accelerated atherosclerosis from birth. The prevalence of heterozygous FH is estimated to be 1 in 200 to 1 in 500[2–4] in unselected community populations, with an estimated 30 million people worldwide, including 3.6 million individuals in the Asia-Pacific region alone. In many countries, less than 1% of patients with FH are reported to be diagnosed.[5]

Despite the increasing recognition of the importance of FH,[6] the care for patients with FH remains suboptimal, particularly in aspects of screening, diagnosis, and treatment of this condition.[7] This may reflect the lack of implementation and organization of evidence-based utilization of services and treatments.[8]

According to international recommendations, effective models of care for FH should include the use of genetic and imaging services, effective cholesterol-lowering therapies, registries, education and training programs, patient support groups, and clinical audit and research.[1,9] However, information on the existing care and services are lacking in the Asia-Pacific region and Southern Hemisphere. Redressing inequalities and imbalances in care and the implementation of effective solutions requires garnering of more knowledge and comparing health care resources in countries across the globe.

We report on the outcomes of an investigation into the diverse aspects of the health care of FH in selected countries in the Asia-Pacific region and the Southern Hemisphere, as well as in the United Kingdom (UK) as a benchmark.

Methods

The present study was undertaken as part of the "Ten Countries Study", a series of translational research projects investigating several aspects of the care of FH.[10–13] The methodology has been as previously described.[10] The countries included in the present study are Australia, China, Hong Kong, Japan, Malaysia, New Zealand, Philippines, Taiwan, and Vietnam that were members of the Asian-Pacific Society of Atherosclerosis and Vascular Disease, and South Africa and Brazil (in the Southern Hemisphere).[14] The UK was used as a reference group to provide benchmark data for international comparison.[10]

Implementation of the survey

The study was based on a series of online questionnaires (Survey Monkey) and phone/email interviews, followed by further email and face-to-face conversations to verify and elaborate on the initial responses; responses were

ascertained from June 2014 to October 2018. The questionnaires investigated a wide range of topics including the availability and implementation of key services and facilities for the care of FH. The enquiry related to the following elements of FH: screening strategies, diagnostic and risk assessment protocols, treatment strategies, genetic testing, imaging and apheresis facilities, management, registries, education/training programs, research activities, and publications. Full details of the original online questionnaires are given in the Supplementary Material. Some of key questions were raised following subsequent emails and face-to-face conversations. The questionnaires were completed by key opinion leaders in each country based on their opinions and any available national surveys. All key opinion leaders were clinicians and lipid specialists with expertise in cardiology, endocrinology, or internal medicine. Their full affiliations are given in the title page of this article.

The responses from the key opinion leaders in each center of excellence were collected and reviewed by three investigators (JP, DC, and GFW). To ensure precision and accuracy, each key opinion leader was provided with summaries of their responses, at each stage, for confirmation. Additional or corroborative information was elicited when responses to the questions were incomplete, inconsistent, or ambiguous. This was undertaken by direct email contact or face-to-face meeting at international conferences. In addition to the surveys, a literature search for FH-related publications (basic science and human studies) was undertaken (DC and JP) to determine the number of FH publication in each participating country. The search used the PubMed database with the search string (title/abstract) "FH", "familial hypercholesterolemia", "familial hypercholesterolaemia", "primary hypercholesterolemia," or "primary hypercholesterolaemia," excluding professional guidelines, reviews, editorials, and commentaries, between January 1991 and December 2017. The first author's affiliation was used to define the country of publication.

Estimations of prevalence and health care expenditure

In estimating the number of patients with FH in each country/region, we assumed a prevalence of 1 in 1,000,000 and 1 in 300 for homozygous and heterozygous FH, respectively, based on published data.[2,3,15,16] Government expenditure on health care in each country or region was retrieved from public domains including Organization for Economic Co-operation and Development,[17] the World Bank Group,[18] and the World Health Organization.[19]

Data analyses

Data were analyzed using SPSS 21 (SPSS, Inc, Chicago, IL). Cohen's kappa coefficient ($\varkappa$) was used to measure the agreements between the amount of government expenditure on health care (expressed in USD dollars), the demonstration of cost-effectiveness for FH screening and treatment, the percentage of people diagnosed with FH, the availability of government reimbursement for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and apheresis, and the percentage of patients with FH achieving LDL cholesterol treatment target, wherever appropriate.

Results

Population statistics and health care expenditure

Table 1 shows the estimated number of patients with FH, the proportion of patients with FH diagnosed, and government expenditure on health care in each of the 12 countries. As anticipated, the estimated number of patients with FH was highest in China. However, the percentage of people diagnosed with FH was low, being $<3\%$ in most countries (Fig. 1). The exceptions were the UK ($\sim 15\%$), South Africa (5.3%), Australia (4.0%), and in Taiwan (3.8%). China, Philippines, and Vietnam had detection rates of $<0.1\%$. The total number of case of homozygous patients with FH identified were as follows: 75 in UK, 40 in Australia, 15 in Brazil, 60 in China, 7 in Hong Kong, 180 in Japan, 41 in Malaysia, 8 in New Zealand, 160 in South Africa, 33 in Taiwan and 10 in Vietnam. Total expenditure per capita on health care in these countries ranged from $117 (Vietnam) to $4934 (Australia), or from 3.9% (Malaysia) to 10.9% (Japan) when expressed as a share of gross domestic product (GDP) spent on health care. The percentage of patients with FH with symptomatic CAD ranged from 5% to 10% (Hong Kong and Vietnam) to 30% (China, New Zealand, Philippines, and Taiwan) with the UK, Australia, Japan, Malaysia, and South Africa showing 15% to 25% of patients with FH. When categorizing the countries according to the percentage of FH diagnosed and health care expenditure (% GDP on health care), using the median values as cutoffs (2.2% and 6.6%, respectively), there was a moderate positive agreement between the percentage of people diagnosed with FH and government expenditure on health care ($\varkappa = 0.667$, $P < .05$).

Availability of guidelines and screening strategies

Table 2 summarizes the availability of national detection guidelines on FH and use of screening strategies for FH in the countries. All countries had an established Heart Foundation (or related organization). Of them, 8 countries (UK, Australia, Brazil, China, Hong Kong, Japan, New Zealand, and Taiwan) had written national guidelines and protocols for FH management. For screening strategies, opportunistic and cascade approaches were commonly used for FH screening (8 of 12 countries). Opportunistic screening

Table 1 Population size, estimated number of patients with FH, percentage of FH diagnosed, prevalence of coronary artery disease and total expenditure on health care across the countries

Country	Population* (millions)	Estimated number of FH†			% FH diagnosed‡	Total expenditure per capita ($) on health care*	% Gross domestic product on health care*
		Homozygotes		Heterozygotes			
		1/1,000,000	1/300,000	1/300			
United Kingdom	66	66	217	220,000	10–20	4356	9.9
Australia	24	24	79	80,000	4	4934	9.5
Brazil	207	207	683	700,000	2.9	780	8.9
China	1400	1400	4600	4,600,000	<0.1	426	5.3
Hong Kong	7.3	7	23	24,000	2.2	2208	5.7
Japan	128	128	422	423,000	1	3733	10.9
Malaysia	32	32	107	107,000	1.4	377	3.9
New Zealand	4.7	5	17	16,000	2.5	3554	9.3
Philippines	103	103	340	340,000	<0.1	121	4.4
South Africa	56	56	185	190,000	5.3	471	8.2
Taiwan	24	24	79	80,000	3.8	2546	6.6
Vietnam	95	95	314	310,000	<0.1	117	5.7

*Based on 2016 data.

†Estimated number of patients with FH based on a prevalence rate of homozygous (1/1,000,000 and 1/300,000) and heterozygous FH (1/300) in the general population.

‡Percentage of FH diagnosed was based on the estimated number of patients with FH identified using phenotypic criteria and/or genetic testing by the key opinion leaders in each country; this was based on the estimated total number of heterozygous FH assuming a prevalence rate of 1/300.

was not carried out in China and cascade screening was not practiced in South Africa and Taiwan. However, universal screening for FH was not practiced in any of the countries.

Phenotypic criteria for diagnosis

Table 3 shows the reported use of phenotypic criteria and genetic testing for the diagnosis of FH in the countries. The Dutch Lipid Clinic Network (DLCN) criteria was the most commonly employed criteria for FH diagnosis (9 of the 12 countries: UK, Australia, Brazil, Hong Kong, New Zealand, Malaysia, Philippines, Taiwan, and Vietnam). The Simon Broome criteria were only used in the UK and Malaysia. The MEDPED and DLCN criteria were both used in the Philippines. The UK, China, Japan, and South Africa used country-specific diagnostic criteria. Genetic testing was available in specialized centers in most countries, with the exception of the Philippines and Vietnam. However, genetic testing was mainly employed within the research setting.

FH diagnoses were primarily made using phenotypic criteria alone in almost all countries, with the exception of Brazil that reported 75% uptake of the combined phenotypic and genetic criteria to diagnose FH. A relatively high percentage of genetic diagnosis of FH in Vietnam was achieved by a recent international initiative with a research center in Australia.[27] Combined phenotypic and genetic criteria were used to diagnose 20% to 30% of cases in UK, Australia, Japan, Malaysia, New Zealand, South Africa, and Taiwan, and 10% in China and Hong Kong.

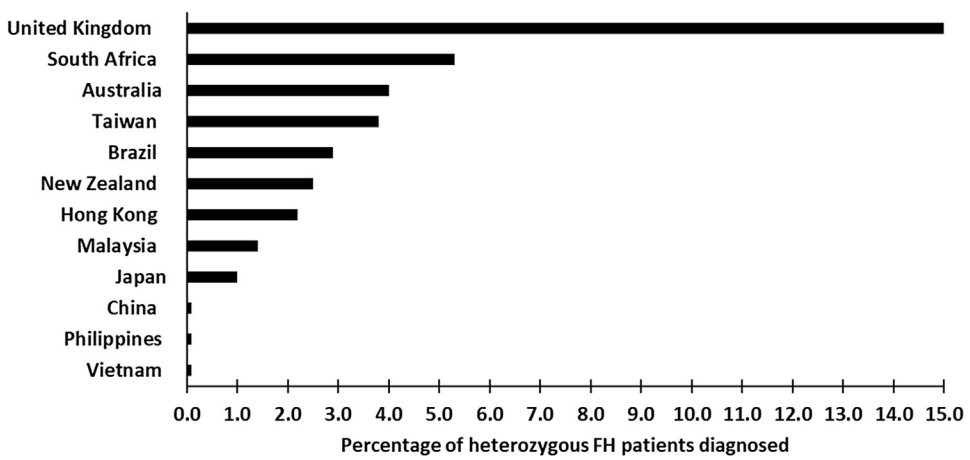

Figure 1 Patients diagnosed with FH as a percentage of estimated total number of patients in the countries.

Table 2 Heart foundations, guidelines, and screening strategies for FH used in the countries

Country	Heart foundation or related organization	National guidelines on FH	Screening strategies employed to detect FH		
			Opportunistic	Systematic	Universal
United Kingdom	Yes	Yes	Yes	Yes	No
Australia	Yes	Yes	Yes	Yes	No
Brazil	Yes	Yes	Yes	Yes	No
China	Yes	Yes*	No	Yes	No
Hong Kong	Yes	Yes*	Yes	Yes	No
Japan	Yes	Yes	Yes	Yes	No
Malaysia	Yes	No	Yes	Yes	No
New Zealand	Yes	Yes	Yes	Yes	No
Philippines	Yes	No	Yes	Yes	No
South Africa	Yes	No	Yes	No	No
Taiwan	Yes	Yes*	Yes	No	No
Vietnam	Yes	No	Yes	Yes	No

*National guidelines/consensus statement on FH were recently published from Taiwan (2017),[20] China (2018)[21] and Hong Kong (2018).[22]

Cardiovascular risk assessment

As seen in Supplementary Table 1, smoking, hypertension, obesity, and diabetes were used for cardiovascular risk assessment of patients with FH in all countries, with the exception of China that did not account for obesity and diabetes. However, a diagnosis of depression was not used in risk assessment except in the UK, Australia, and

Table 3 Phenotypic definitions for FH, availability of genetic testing, and proportion of patients diagnosed by phenotypic criteria and genetic testing in the countries

Country	Phenotypic Criteria*,†				Genetic Testing	Estimated % FH diagnosed by	
	DLCN	Simon Broome	MEDPED	Other		Phenotypic criteria alone	Phenotypic criteria + genetic testing
United Kingdom	Yes	Yes	No	Yes‡	Yes	80	20
Australia	Yes	No	No	No	Yes	70	30
Brazil	Yes	No	No	No	Yes	25	75
China	No	No	No	Yes§	Yes	90	10
Hong Kong	Yes‖	No	No	No	Yes	90	10
Japan	No	No	No	Yes	Yes	80	20
Malaysia	Yes	Yes	No	No	Yes	75	25
New Zealand	Yes	No	No	No	Yes	70	30
Philippines	Yes	No	Yes	No	No	>95	<5
South Africa	No	No	No	Yes	Yes¶	80	20
Taiwan	Yes	No	No	No	Yes	70	30
Vietnam	Yes	No	No	No	Yes#	15	85

DLCN, Dutch Lipid Clinic Network; LDL, low-density lipoprotein; MEDPED, Make Early Diagnosis to Prevent Early Deaths Diagnostic.

*Phenotypic criteria for children: There are no standardized, international criteria for defining pediatric FH. However, the diagnosis is generally based on an LDL cholesterol ≥5.0 mmol/L, or an LDL cholesterol ≥3.5 mmol/L plus a family history of premature CHD and/or baseline high cholesterol in one parent and/or an FH-causing mutation.[23] The diagnosis may also be defined according to specific age- and gender-specific LDL cholesterol cutoffs, particularly during cascade testing.[24]

†Phenotypic criteria for homozygous FH: There are no standardized, international criteria for defining homozygous FH. However, the diagnosis is generally based on genetic confirmation of genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus, and/or an untreated LDL cholesterol >13 mmol/L (>10 mmol/l in Japan) or treated LDL cholesterol ≥8 mmol/L together with either cutaneous/tendon xanthoma before age 10 y or heterozygous FH in both parents.[16,25].

‡Wales FH Service Scoring Criteria.[26]

§Based on the National consensus statement on FH (2018).[21]

‖DLCN phenotypic criteria with a lower threshold for LDL cholesterol levels.

¶With research funding alone.

#With international assistance.

Table 4 Dietary, drug, and apheresis treatments for patients with FH in the countries

Country	Low saturated fat diet	Statins		Ezetimibe	Resins	Niacin	Probucol	Apheresis
		Adults	Children*					
United Kingdom	Yes	Yes	Yes (8 y)	Yes	Yes	No	No	Yes
Australia	Yes	Yes	Yes (10 y)	Yes	Yes	Yes	No	Yes
Brazil	Yes	Yes	Yes (8 y)	Yes	No	Yes	No	Yes
China	Yes	Yes	Yes (10 y)	Yes	No	No	Yes	No†
Hong Kong	Yes	Yes	Yes (15 y)	Yes	Yes	No	No	No‡
Japan	Yes	Yes	Yes (15 y)	Yes	Yes	Yes	Yes	Yes
Malaysia	Yes	Yes	Yes (8 y)	Yes	Yes	No	No	Yes
New Zealand	Yes	Yes	Yes (10 y)	Yes	Yes	No	No	Yes
Philippines	Yes	Yes	No§	Yes	No	Yes	No	No
South Africa	Yes	Yes	Yes (8 y)	Yes‖	No	No	No	Yes
Taiwan	Yes	Yes	Yes (8 y)	Yes	Yes	Yes	No	Yes¶
Vietnam	Yes	Yes	Yes (5 y)	Yes	Yes	Yes	No	No†

*Earliest age that statin is registered for children with heterozygous FH in brackets.
†Apheresis facilities available in these countries, but services are limited owing to lack of government support and/or reimbursement by insurers.
‡Plasmapheresis carried out with government funding in a small number of homozygous patients in few hospital in Hong Kong.
§No statins employed to treat children owing to lack of government reimbursement.
‖Use limited to patients with LDL cholesterol >5.0 mmol/L.
¶Funded by general medical insurance.

Taiwan. Lipoprotein(a) [Lp(a)] was also included in risk assessment in most of the countries except Hong Kong, Philippines, and Vietnam. While imaging facilities were available in all countries, coronary artery calcium (CAC) and carotid intima-media thickness/plaque were not routinely used to assess cardiovascular risk in the UK, Hong Kong, Malaysia, and New Zealand.

Dietary, drug, and apheresis treatments

The current dietary and therapeutic approaches for treating patients with FH in the countries are summarized in Table 4. As expected, low saturated fat diet, statins, and ezetimibe were the first-line therapies universally provided to all patients with FH. With the exception of the Philippines, statins were routinely prescribed for children in all countries. Resins were widely used in most of the countries, including the UK, Australia, Hong Kong, Japan, Malaysia, New Zealand, Taiwan, and Vietnam. By contrast, Japan was the only country to prescribe both niacin and probucol for patients with FH. Lipoprotein apheresis was available in all countries except the Philippines, but was only utilized in the UK, Australia, Brazil, Japan, Malaysia, New Zealand, South Africa, and Taiwan for homozygous FH and severe heterozygous FH. Lipoprotein apheresis in China, Hong Kong, and Vietnam was limited owing to a lack of government support and/or reimbursement by insurers.

Details of apheresis in eight countries

Table 5 summarizes the types and frequency of apheresis, factors affecting the use of apheresis, and main adverse effects in eight countries, where this treatment was practiced. Cascade filtration was most commonly used, with plasmapheresis exclusively used in Brazil, South Africa, and Taiwan. Of these countries, dextran sulfate adsorption was only used in Japan. Major factors affecting the use of apheresis included a lack of local experience/support, government support and reimbursement by insurers. Despite most countries offering to treat patients with apheresis during pregnancy, Malaysia, New Zealand, and South Africa reported that women often refused this treatment during pregnancy. Apheresis was offered to children in the UK, Australia, Japan, New Zealand, South Africa, and Taiwan. Main adverse effects reported with apheresis included difficulty with vascular access, iron/vitamin/mineral deficiency, low blood pressure, nausea/vomiting, and hemorrhage near injection site.

Use of PCSK9 inhibitors

Table 6 details the use of PCSK9 inhibitors for treating patients with FH in the countries. While as of November 2018, PCSK9 inhibitors were registered for clinical use in 7 countries, government reimbursement was only available for patients with homozygous FH in the UK, Australia, Japan, and Taiwan. The UK and Australia were the only country providing government reimbursement for PCSK9 inhibitors to both homozygous and heterozygous FH patients. PCSK9 inhibitors were used in 5%–10% of patients with FH in most countries, except Hong Kong (1%–5%), and not registered or available in China, Philippines, and Vietnam. There was no significant association between government expenditure on health care (as a share of GDP) and the availability of government reimbursement for PCSK9 inhibitors ($\varkappa = 0.333$, $P > .05$).

Table 5 Indications, types, use, and side-effects of apheresis in eight countries with available facilities

Country	Indications for apheresis	Type of apheresis	Frequency	Factors affecting the use of apheresis	Offered during pregnancy	Offered to children	Main adverse effects reported
United Kingdom	HoFH HeFH with progressive CHD* A reduction in LDL cholesterol of <50% or LDL cholesterol >5 mmol/L† Heart UK guideline	Cascade filtration, plasmapheresis	weekly/fortnightly	Patient refusal to receive treatment Lack of local experience and support Limited number of apheresis centers	Yes	Yes	Difficulty with vascular access Iron/vitamin/minerals deficiency Anemia
Australia	HoFH HeFH with progressive CHD*	Cascade filtration	fortnightly	Patient refusal to receive treatment Lack of local experience and support	Yes	Yes	Difficulty with vascular access Iron/vitamin/minerals deficiency Anemia Citrate toxicity Venous thrombosis shunt
Brazil	As per FDA indications	Plasmapheresis	fortnightly	Lack of government subsidies Lack of insurance reimbursement Apheresis only performed in one lipid clinic	No	No	Low blood pressure
Japan	HoFH HeFH with progressive CHD*	Dextran sulfate	weekly/fortnightly	Patient refusal to receive treatment Lack of government subsidies for HeFH	Yes	Yes	Difficulty with vascular access Low blood pressure Hemorrhage near injection site
Malaysia	HoFH HeFH with progressive CHD*	Cascade filtration	2–4 weekly	Patient refusal to receive treatment Lack of government subsidies Lack of insurance reimbursement	Yes‡	No	Difficulty with vascular access Low blood pressure Nausea/vomiting
New Zealand	HoFH HeFH with progressive CHD*	Cascade filtration	2–4 weekly	Patient refusal to receive treatment Lack of government subsidies Lack of insurance reimbursement	Yes‡	Yes	Iron/vitamin/minerals deficiency Hemorrhage near injection site Nausea/vomiting
South Africa	HoFH	Plasmapheresis	fortnightly	Patient refusal to receive treatment Lack of government subsidies Lack of insurance reimbursement Lack of local experience and support	Yes‡	Yes	Tiredness
Taiwan	HoFH	Plasmapheresis	weekly	Patient refusal to receive treatment	No	Yes	Difficulty with vascular access

HoFH, homozygous familial hypercholesterolemia (including compound heterozygous familial hypercholesterolemia); HeFH, heterozygous familial hypercholesterolemia; LDL, low-density lipoprotein.
*HeFH with progressive CHD, who are refractory or intolerant to maximal pharmacotherapy.
†HeFH who are on diet and maximally tolerated drug treatment.
‡Apheresis was not yet performed because of lack of FH pregnancy cases or patients refusal of treatment.

Table 6 Registration, reimbursement and use of PCSK9 inhibitors for treating FH in different countries

Country	Registered for clinical use	Government reimbursement		% diagnosed patients with FH treated with PCSK9 inhibitors
		HoFH	HeFH	
United Kingdom	Yes	Yes	Yes	5%–10%
Australia	Yes	Yes	Yes	5%–10%
Brazil	Yes	No	No	5%–10%
China	Yes*	No	No	0%
Hong Kong	Yes	No	No	1%–5%
Japan	Yes	Yes	No	5%–10%
Malaysia	Yes	No	No	5%–10%
New Zealand	No†	No	No	5%–10%
Philippines	No	No	No	0%
South Africa	No†	No	No	5%–10%
Taiwan	Yes	Yes‡	No	5%–10%
Vietnam	No	No	No	0%

*Registered but not available for use as of October 2018.
†PCSK9 inhibitors only available as part of clinical trials as of December 2018.
‡Taiwan National Health Insurance.

LDL cholesterol treatment targets

Figure 2 shows the percentage of patients with FH achieving LDL cholesterol targets in the countries. UK had the highest percentage of patients with FH achieving the LDL cholesterol treatment targets of <2.5 mmol/L (70%) and <1.8 mmol/L (25%).[3,5] Less than 5% of patients in Brazil, China, Japan, Malaysia, South Africa and, Vietnam were reported as achieving an LDL cholesterol treatment target of <1.8 mmol/L. When categorizing the countries according to the percentage of patients with FH achieving an LDL cholesterol treatment target of <2.5 mmol/L, there was a moderate positive agreement between the percentage of patients with FH achieving the target and government reimbursement for PCSK9 inhibitors ($\varkappa = 0.667$, $P < .05$) and expenditure on health care ($\varkappa = 0.500$, $P = .079$).

Primary and pediatric care, telehealth service, and patient support group

The availability and use of primary (general practice) and pediatric care, telehealth services, and patient support groups in the countries are shown in Supplementary Table 2. Primary care for FH was practiced in all countries, with the exception of Hong Kong and South Africa, where care was provided by specialists alone. Of the 12 countries, UK, Australia, China, Japan, Malaysia, Taiwan, and Vietnam reported providing specific services for children with FH. Telehealth services for FH were only available in

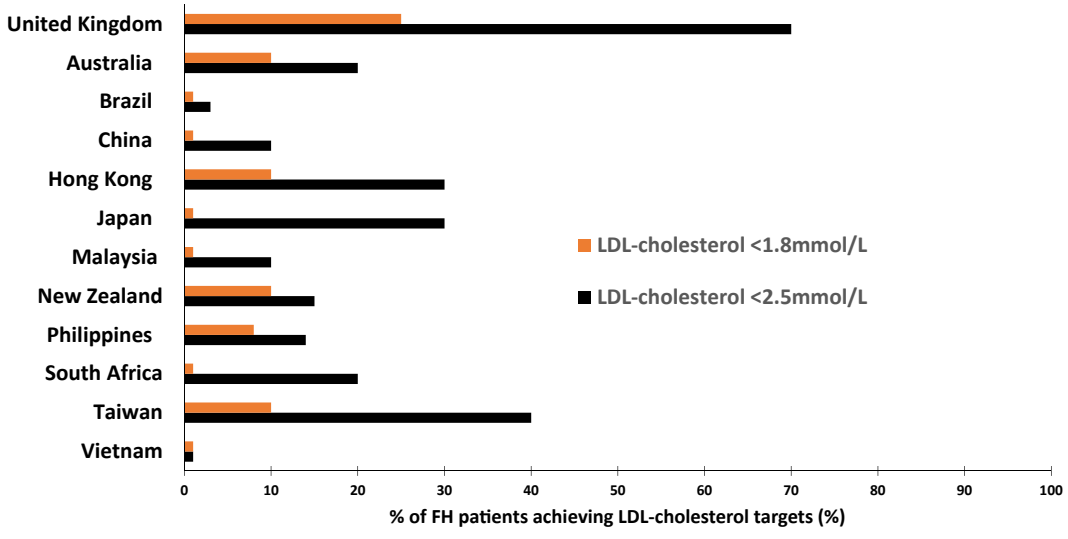

Figure 2 Percentage of patients with FH achieving LDL cholesterol target in different countries. FH, familial hypercholesterolemia; LDL, low-density lipoprotein.

Table 7 Registries, education/training, research activities, and number of published works relating to FH in different countries

Country*	National registry	Education/training program†	Research activities						Number of publications‡
			Basic science	Human studies	Types of Human Studies				
					Metabolic	Genetic	Epidemiological/ clinical	Clinical trial	
United Kingdom	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	30–50
Australia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	30–50
Brazil	No	Yes	No	Yes	Yes	Yes	Yes	Yes	30–50
China	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	50–70
Hong Kong	No	No	No	Yes	No	Yes	Yes	Yes	<10
Japan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100–120
Malaysia	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	20–30
New Zealand	No	No	Yes	Yes	No	Yes	Yes	Yes	10–20
Philippines	No	No	No	Yes	No	Yes	No	No	<10
South Africa	No	Yes	No	Yes	No	Yes	Yes	Yes	50–70
Taiwan	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	20–30
Vietnam	No	Yes	No	Yes	Yes	Yes	No	Yes	<10

*All countries are members of Familial Hypercholesterolaemia Studies Collaboration (FHSC).

†Education or training programs on FH for physicians, nurses or laboratory staff.

‡A literature review for FH research (basic science and human studies) was performed using the PubMed database between January 1991 to December 2017 with the search string (title/abstract) "FH", "familial hypercholesterolaemia", "familial hypercholesterolemia", "primary hypercholesterolemia" or "primary hypercholesterolemia" excluding professional guidelines, reviews, editorials and commentaries. The first author's affiliation was used to define the country of publication.

Australia and China, and patient support groups in the UK, Australia, Japan, and Taiwan.

Availability of national registry, education, and research programs

Table 7 details the availabilities of national FH registries, education/training programs, research activities, and the number of published works relating to FH in the countries. National registries had been established in the UK, Australia, Japan, Malaysia, and Taiwan. Education/training programs were provided to physicians, nurses, and laboratory staff in UK, Australia, Brazil, China, Japan, South Africa, Taiwan, and Vietnam. All countries were members of Familial Hypercholesterolaemia Studies Collaboration,[15] with research studies relating primarily to genetics, epidemiology, and clinical trials. Japan had the highest number of published works, mainly on clinical trials (>100) during 1991 to 2017, followed by China (mainly genetic studies), South Africa, UK, Australia, Brazil, Malaysia, and Taiwan (20–70 publications). However, the number of published works were <10 in Hong Kong, New Zealand, Philippines, and Vietnam.

Health economic analyses and subsidies/ reimbursements

Table 8 summarizes the use of health technology assessment (ie, inclusion of health economic analyses) and the availability of subsidies/reimbursement for cascade screening, genetics testing and apheresis in the countries. Health technology assessments for pricing and reimbursement for health service are performed in UK, Australia, Brazil, China, Japan, Malaysia, and Taiwan. However, cost-effectiveness analyses of screening and/or treatment in FH were only carried out in the UK, Australia, and Japan. Subsidies/reimbursements for cascade screening, genetic testing, and apheresis by state/region and/or government were only available in the UK, Australia, and New Zealand. Japan received state/regional support only for cascade screening. There was a positive agreement between the demonstration of the cost-effectiveness of FH screening and the availability of subsidies for cascade screening ($\varkappa = 0.571$, $P < .05$) and genetic testing ($\varkappa = 0.750$, $P < .01$). Likewise, there was a significant positive agreement between the demonstration of cost-effectiveness of FH treatment and subsidies for PCSK9 inhibitors ($\varkappa = 0.800$, $P < .01$) and apheresis ($\varkappa = 0.636$, $P < .05$) for treating FH.

Discussion

The present study is the first to investigate the services and facilities for the care of FH across several countries in the Asia-Pacific region and South Hemisphere. Although the UK, Australia, and Japan are providing FH patients with relatively better services and facilities, FH remains largely underdiagnosed and inadequately treated, particularly in less economically developed countries, such as the Philippines and Vietnam.

Population statistics and health care expenditure

The overall percentage of patients diagnosed with FH in most of the countries was low compared with the UK, as well as other countries with established cascade screening program

Table 8 Health economic analyses and subsidies/reimbursements for cascade screening, genetic testing, and apheresis in the different countries

Country	Health technology assessments on pricing and reimbursement for health service	Cost-effectiveness analysis of the care of FH		Subsidies/reimbursements		
		Screening	Treatment	Cascade screening	Genetic testing	Apheresis
United Kingdom	Yes	Yes	Yes	State/regional	State/regional	State/regional
Australia	Yes	Yes	Yes	State/regional	State/regional	Government
Brazil	Yes	No	No	Tax reducing program*	Tax reducing program*	No
China	Yes	No	No	Research Institute/University	Research Institute/University	No
Hong Kong	No	No	No	Research Institute/University	Research Institute/University	No
Japan	Yes	No	Yes	State/regional	Hospital	Government (for hoFH)
					Research Institute/University	Health insurance (for heFH)
Malaysia	Yes	No	No	Government	Research Grants	Government (for hoFH)
				Research Institute/University		Charity
New Zealand	No	No	No	State/regional	State/regional	State/regional
Philippines	No	No	No	No	No	No
South Africa	No	No	No	No	Research Institute/University	State/regional
						Health insurance
Taiwan	Yes	No	No	No	Health organization†	Health insurance
Vietnam	No	No	No	Health insurance Charity	No	No

HoFH, homozygous familial hypercholesterolemia (including compound heterozygous familial hypercholesterolemia); HeFH, heterozygous familial hypercholesterolemia.

*Tax incentive program offered by the federal government of Brazil to FH services for cascade screening and genetic testing (eg, a private hospital subsides the cascade screening via the lipid clinic, as a consequence is less liable for tax).

†Taiwan Society of Lipids and Atherosclerosis.

implemented.[28] This concurs with earlier reports, reflecting the underdiagnosis of FH in Asia-Pacific countries.[5] The detection of FH across the countries was also associated with lower government expenditure on health care. This observation underscores the need for explicit government funding policy and public funding to improve the diagnosis of FH.

The proportion of cases of homozygous FH reported across the countries was generally higher than previously estimated.[15,16] As shown elsewhere,[29] many of these cases are likely to have compound or double heterozygous FH.

Availability of guidelines and screening strategies

Systematic (cascade) testing of family members of known index cases of FH is cost-effective in detecting FH[30] but this requires initial identification of index cases, which usually entails opportunistic screening. Consistent with this, both systematic and opportunistic detection strategies for FH screening were widely deployed in most of the 12 countries. While universal lipid screening is recommended by expert opinions,[31,32] none of the 12 countries implemented it for FH screening, probably owing to acceptability and feasibility issues, although recent evidence has testified to its value.[33–35]

Phenotypic criteria for diagnosis

The DLCN criteria were the most commonly used criteria for FH diagnosis across the countries. This concurs with our recent findings that the phenotypic DLCN definite FH had a better balance between sensitivity and specificity than phenotypic Simon Broome and MEDPED criteria in detecting a mutation.[36] Although genetic testing for FH was available in most countries, the overall percentage of FH diagnosed by a combination of phenotypic criteria and genetic testing across the countries was low. The exception was Brazil, but this was likely to be driven by a regional-specific genetic cascade screening program in the state of Sao Paulo since 2010.[37] The reasons for the infrequent use of genetic testing for FH diagnosis among the countries are complex and may be principally driven by costs[38] and

possibly cultural issues.[39] In respect of the need to standardize the diagnosis of homozygous FH, we propose that use of the IAS definition for severe FH could provide a solution; recent data show that this definition predicts CAD mortality in patients with a definite diagnosis of FH.[40,41]

Cardiovascular risk assessment

While conventional cardiovascular risk assessment, such as Framingham risk score, is not appropriate in FH, inclusions of modifiable factors in cardiovascular risk assessment remains important for treatment decision in addition to LDL cholesterol lowering.[1,42] This notion is consistent with our findings that smoking, hypertension, obesity, and diabetes were included in risk assessment across the countries/regions. Depression is known to have an adverse impact on cardiovascular disease (CVD) and health-related quality of life,[43] but was only carried out in the UK, Australia, and Taiwan. Whether depression predisposes affected individuals to poor adherence to treatment merits investigation.[13] Recent studies suggest that elevated Lp(a) remains a risk factor in FH[44,45] despite reduction of LDL cholesterol with statins.[46] That two-thirds of the countries included elevated Lp(a) in their risk assessment highlights their perception of elevated Lp(a) as a risk factor in FH. However, reliable measurement of Lp(a) and its impact on measured LDL cholesterol for risk assessment and intervention efficacy remains a challenge.[47] Likewise, CAC and plaque formation are known to be strong predictors of atherosclerotic CVD, especially in asymptomatic FH patients,[48,49] but only half of the countries included both CAC and carotid intima-media thickness/plaques in their risk assessment of FH. This underscores a need to increase use of these imaging methods, as precision medicine tools, in risk assessment in FH.

Dietary, drug, and apheresis treatments

FH is associated with a high risk of atherosclerotic CVD and requires aggressive treatment through a combination of lifestyle modifications and high-intensity LDL cholesterol–lowering therapy.[1] Treatment strategies appropriately included a low saturated fat diet, statins, and ezetimibe, consistent with current guidelines for FH.[1] The uses of resins, niacin, and probucol varied greatly across the countries. While apheresis is safe and effective in reducing LDL cholesterol in patients with homozygous FH or when drug therapy is inadequate in reducing LDL cholesterol to target levels,[50] the use of apheresis services was limited in most of these countries probably owing to substantial costs that were not covered by government support or reimbursement by insurers (Table 5). Improving the use of apheresis through patient education and local training is important to close the treatment gaps in this area. PCSK9 inhibitors were registered for use in most countries. However, the proportion of patients with FH treated with PCSK9 inhibitors was generally low, owing to high cost and restricted government reimbursement.[51] Lack of accessibility to PCSK9 inhibitors may contribute to patients with FH not achieving LDL cholesterol treatment targets.

Primary and pediatric care, telehealth service, and patient support group

Models of care for FH ideally entail multidisciplinary providers and patient support groups.[52,53] This includes shared care with primary care and specialist pediatric clinics, and a telehealth services for remote areas. Patient support groups are important to improve information, communication and support services for patients and families with FH. We emphasize the need for better coordination to standardize the shared care services and awareness of the importance of telehealth services and patient support groups in improving the care for FH.[53,54]

Availability of national registry, education, and research programs

Improving the quality of care of FH requires implementation of evidence-based interventions. This can be enabled by clinical registries, continuing education/training of all health care providers, and ongoing research and audit in FH. The UK, Australia, and Japan have implemented FH registries, education/training programs and undertaken research. These activities were notably suboptimal in less economically developed countries, such as the Philippines and Vietnam. Development of closer regional and international collaboration on genetic services, research, and education/training programs between countries could greatly enhance the quality of services for FH where gaps are identified.

Health economic analyses and subsidies/ reimbursements

The use of health technology assessment on pricing and reimbursement for health service was under-recognized in most of the assessed countries. We found significant agreements between the demonstration of cost-effectiveness of the screening and treatment in FH and the subsidisation/reimbursements for cascade screening, genetic testing, and PCSK9 inhibitors/apheresis. These observations suggest that cost-effectiveness analyses are an important tool to provide better evidence advocating for government subsidies and reimbursements in the care of FH.

Study limitations

Study limitations include the accuracy and reliability of the responses of the selected key opinion leaders, who were based in centers of excellence in their respective countries. Responses might have been biased and not captured real deficits in services and facilities across the countries. The methodology used, however, recapitulates that used in other surveys and was also based on available national studies.[15]

However, the investigators considered that their responses were generally concordant in the views of other national experts. The percentage of people with diagnosed FH identified in each country was based on a prevalence rate of 1/300. This is generally comparable with the existing prevalence data for heterogeneous FH in the UK (1 in 273), Australia (1 in 250–350), Brazil (1 in 263), and China (1 in 250-350).[2,3,55,56] However, our 1 in 300 estimation may not accurately reflect the true FH prevalence in countries such as South Africa, where gene founder effects may occur in selected groups in the population.[57] A prevalence of 1 in 208 was reported in the Hokuriku District of Japan using the Hardy–Weinberg equilibrium, which has also been suggested to reflect a possible founder effect.[58]

Conclusion

The present study identified important deficits in the detection and treatment of FH, in the care of FH across countries in the Asia-Pacific region and Southern Hemisphere. The UK, Australia, and Japan appeared to provide better services and facilities to patients with FH. Major FH detection and treatment gaps were identified in countries that are less economically developed, including the Philippines and Vietnam. Implementation of health technology assessment for the care of FH is important to enhance funding support from government and industries to improve the accessibility to genetic testing and wider uses of advanced drug and apheresis treatment in these countries. Further collaborative efforts with countries in Europe and North America or other international initiatives, such as Familial Hypercholesterolaemia Studies Collaboration,[15] are also important.

The implementation of recommendations for improving the care of FH in the countries included in this study involves several generic strategies.[59–61] This requires a combination of approaches involving government and health care organizations, on the one hand, and patients, providers, and communities, on the other. At the top level is the establishment of government policy and support from public funding. At the middle level is the improvement of the efficiency of organizations, such as health care systems. At the lowest level is the strengthening of the capabilities of patients and health care providers. Empowering communities and multiple stakeholders to recognize the importance of detecting and treating elevated cholesterol in the context of a family history of premature coronary disease is also critical. Updating of the World Health Organization recommendations[62] on FH is an essential first step to the global implementation of improved care of patients and families with FH.

Acknowledgments

Authors' contributions: GFW, SY, BT, HS, RDS, THT, LGS, HMN, ADM, JL, and PMG were investigators who contributed to the concept or design of the study. JP, DC, MH, LAU, SK, MJC, CMF, DDL, TCS, ZA, and GFW contributed to data acquisition in the "Ten Countries Study". JP, DC, ZA, and GFW contributed to the statistical analyses. All authors contributed to the interpretation of data and critically reviewed and edited the manuscript. All authors approved the final version. In addition, all authors had full access to the study data and were responsible for the final decision to submit the manuscript and are accountable for the accuracy and integrity of the submitted work.

This work was completed as part of the "Ten Countries Study", which was supported by the International Atherosclerosis Society and Pfizer Independent Grants for Learning & Change (Grant ID: 10839501).

Financial disclosures

Conflict of interest: ADM has done investigations and consultations for Amgen, Bayer, Bristol Myers Squibb, MSD, Novartis, Pfizer, Sanofi-Regeneron, Takeda, Warner Lambert. RDS has received personal fees from Amgen, Aegerion, AstraZeneca, Akcea, Biolab, Boehringer-Ingelheim, Cerenis, Eli-Lilly, Genzyme, Kowa, Merck, Pfizer, Sanofi-Regeneron, Torrent, and Unilever. HS reports research grants from Alexion, Amgen, MSD, and Pfizer and personal fees and education grants from Aegerion, Amgen, Janssen Cilag Ltd, MSD, Pfizer, Novo Nordisk and Sanofi. BT reports grants and personal fees from Amgen; grants from AstraZeneca, Merk Sharp & Dohme, Novartis, Pfizer and Roche; personal fees from Merck Serono and Sanofi. SY reports grants and personal fees from Kowa, Otsuka, Shionogi, Bayer Yakuhin, MSD, Takeda, Sanwa Kagaku Kenkyusho, Astellas, Daiichi-Sankyo, AstraZeneca and Kaken; grants from Nippon Boehringer Ingelheim, Kyowa Medex, Mochida, Hayashibara, Teijin, Kissei and National Institute of Biomedical Innovation and personal fees from Medical Review Co, Skylight Biotech, Pfizer, Bristol-Meyers, Astellas-Amgen, Sanofi, Agerion and Toa Eiyou. GFW reports honoraria for advisory boards and speakers bureau or research grants from Amgen Inc, Sanofi, Regeneron, Kowa, and Genfit. All other authors declare no financial interests or potential conflicts of interest.

Supplementary data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jacl.2019.01.009.

References

1. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the international FH foundation. *Int J Cardiol*. 2014;171:309–325.
2. Shi Z, Yuan B, Zhao D, Taylor AW, Lin J, Watts GF. Familial hypercholesterolemia in China: prevalence and evidence of underdetection and

undertreatment in a community population. *Int J Cardiol*. 2014;174:834–836.
3. Watts GF, Shaw JE, Pang J, Magliano DJ, Jennings GLR, Carrington MJ. Prevalence and treatment of familial hypercholesterolemia in Australian communities. *Int J Cardiol*. 2015;185:69–71.
4. Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open*. 2017;7:e016461.
5. Nordestgaard B, Chapman M, Humphries S, et al. 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.
6. Ray KK, Watts GF. Improving the global care of familial hypercholesterolaemia: starting the ball rolling. *Atherosclerosis*. 2018;277:230–233.
7. Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, et al. Familial hypercholesterolaemia: a global call to arms. *Atherosclerosis*. 2015;243:257–259.
8. Cohen JD, Cziraky MJ, Jacobson TA, Maki KC, Karalis DG. Barriers to PCSK9 inhibitor prescriptions for patients with high cardiovascular risk: results of a healthcare provider survey conducted by the national lipid association. *J Clin Lipidol*. 2017;11:891–900.
9. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia - A scientific statement from the american heart association. *Circulation*. 2015;132:2167–2192.
10. Watts GF, Ding PY, George P, et al. Translational research for improving the care of familial hypercholesterolemia: the "Ten Countries Study" and Beyond. *J Atheroscler Thromb*. 2016;23:891–900.
11. Pang J, Hu M, Lin J, et al. An enquiry based on a standardised questionnaire into knowledge, awareness and preferences concerning the care of familial hypercholesterolaemia among primary care physicians in the Asia-Pacific region: the "Ten Countries Study". *BMJ Open*. 2017;7:e017817.
12. Hagger MS, Hardcastle SJ, Hu M, et al. Health literacy in familial hypercholesterolemia: a cross-national study. *Eur J Prev Cardiol*. 2018;25:936–943.
13. Hagger MS, Hardcastle SJ, Hu M, et al. Effects of medication, treatment, and behavioral beliefs on intentions to take medication in patients with familial hypercholesterolemia. *Atherosclerosis*. 2018;277:493–501.
14. Pang J, David Marais A, Blom DJ, et al. Heterozygous familial hypercholesterolaemia in specialist centres in South Africa, Australia and Brazil: importance of early detection and lifestyle advice. *Atherosclerosis*. 2018;277:470–476.
15. Vallejo-Vaz AJ, De Marco M, Stevens CAT, et al. Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS familial hypercholesterolaemia studies collaboration (FHSC). *Atherosclerosis*. 2018;277:234–255.
16. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the consensus panel on familial hypercholesterolaemia of the European atherosclerosis society. *Eur Heart J*. 2014;35:2146–2157.
17. OECD. General government spending. Available at: https://doi.org/10.1787/a31cbf4d-en. Accessed April 1, 2018.
18. The World Bank. Available at: http://www.worldbank.org/. Accessed April 1, 2018.
19. World Health Organization. Global health observatory indicator views. Available at: http://apps.who.int/gho/data/node.imr.WHS7_113?lang=en. Accessed April 1, 2018.
20. Li Y-H, Ueng K-C, Jeng J-S, et al. 2017 Taiwan lipid guidelines for high risk patients. *J Formos Med Assoc*. 2017;116:217–248.
21. Chinese medical assosiation cardiovascular disease branch, atherosclerosis and coronary heart disease group, editorial board of the Chinese journal of cardiovascular diseases. Familial hypercholesterolemia screening and diagnosis - Chinese expert consensus. *Chin J Cardiol*. 2018;46:99–103.
22. Tomlinson B, Chan J, Chan W, et al. Guidance on the management of familial hypercholesterolaemia in Hong Kong: an expert panel consensus viewpoin. *Hong Kong Med J*. 2018;24:408–415.
23. Wiegman A, Gidding SS, Watts GF, et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36:2425–2437.
24. Starr B, Hadfield SG, Hutten BA, et al. Development of sensitive and specific age- and gender-specific low-density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clin Chem Lab Med*. 2008;46:791–803.
25. France M, Rees A, Datta D, et al. EART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. *Atherosclerosis*. 2016;255:128–139.
26. Haralambos K, Whatley SD, Edwards R, et al. Clinical experience of scoring criteria for familial hypercholesterolaemia (FH) genetic testing in wales. *Atherosclerosis*. 2015;240:190–196.
27. Truong TH, Kim NT, Nguyen MNT, et al. Homozygous familial hypercholesterolaemia in Vietnam: case series, genetics and cascade testing of families. *Atherosclerosis*. 2018;277:392–398.
28. Louter L, Defesche J, Roeters van Lennep J. Cascade screening for familial hypercholesterolemia: practical consequences. *Atheroscler Suppl*. 2017;30:77–85.
29. Sjouke B, Kusters DM, Kindt I, et al. Homozygous autosomal dominant hypercholesterolaemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. *Eur Heart J*. 2015;36:560–565.
30. Ademi Z, Watts GF, Pang J, et al. Cascade screening based on genetic testing is cost-effective: evidence for the implementation of models of care for familial hypercholesterolaemia. *J Clin Lipidol*. 2014;8:390–400.
31. Goldberg AC, Hopkins PN, Toth PP, et al. 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;5:133–140.
32. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213–S256.
33. Morris JK, Wald DS, Wald NJ. The evaluation of cascade testing for familial hypercholesterolemia. *Am J Med Genet A*. 2012;158:78–84.
34. McKay AJ, Hogan H, Humphries SE, Marks D, Ray KK, Miners A. Universal screening at age 1–2 years as an adjunct to cascade testing for familial hypercholesterolaemia in the UK: a cost-utility analysis. *Atherosclerosis*. 2018;275:434–443.
35. Klančar G, Grošelj U, Kovač J, et al. Universal screening for familial hypercholesterolemia in children. *J Am Coll Cardiol*. 2015;66:1250–1257.
36. Chan DC, Pang J, Hooper AJ, et al. A comparative analysis of phenotypic predictors of mutations in familial hypercholesterolemia. *J Clin Endocrinol Metab*. 2018;103:1704–1714.
37. Jannes CE, Santos RD, de Souza Silva PR, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. *Atherosclerosis*. 2015;238:101–107.
38. Nordestgaard BG, Benn M. Genetic testing for familial hypercholesterolaemia is essential in individuals with high LDL cholesterol: who does it in the world? *Eur Heart J*. 2017;38:1580–1583.
39. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. *J Am Coll Cardiol*. 2018;72:662–680.
40. Santos RD, Gidding SS, Hegele RA, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International atherosclerosis society severe familial hypercholesterolemia panel. *Lancet Diabetes Endocrinol*. 2016;4:850–861.

41. Humphries SE, Cooper JA, Capps N, et al. Coronary heart disease mortality in severe vs. non-severe familial hypercholesterolaemia in the Simon Broome Register. *Atherosclerosis*. 2019;281:207–212.
42. Pérez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry. *Circulation*. 2017;135:2133–2144.
43. Akioyamen LE, Genest J, Shan SD, Inibhunu H, Chu A, Tu JV. Anxiety, depression, and health-related quality of life in heterozygous familial hypercholesterolemia: a systematic review and meta-analysis. *J Psychosom Res*. 2018;109:32–43.
44. Langsted A, Kamstrup PR, Benn M, Tybjærg-Hansen A, Nordestgaard BG. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4:577–587.
45. Chan DC, Pang J, Hooper AJ, et al. Elevated lipoprotein(a), hypertension and renal insufficiency as predictors of coronary artery disease in patients with genetically confirmed heterozygous familial hypercholesterolemia. *Int J Cardiol*. 2015;201:633–638.
46. Watts GF, Boffa MB. Lipoprotein (a): lodestar for future clinical trials. *Lancet*. 2018;392:1281–1282.
47. Yeang C, Witztum JL, Tsimikas S. 'LDL-C' = LDL-C+ Lp (a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. *Curr Opin Lipidol*. 2015;26:169–178.
48. Sijbrands EJ, Nieman K, Budoff MJ. Cardiac computed tomography imaging in familial hypercholesterolemia: implications for therapy and clinical trials. *Curr Opin Lipidol*. 2015;26:586–592.
49. de Isla LP, Alonso R, Muñiz-Grijalvo O, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. *J Clin Lipidol*. 2018;12:948–957.
50. Stefanutti C, Julius U, Watts GF, et al. Toward an international consensus—Integrating lipoprotein apheresis and new lipid-lowering drugs. *J Clin Lipidol*. 2017;11:858–871.e853.
51. Watts GF, Norman R. Squaring up the health economics of PCSK9 monoclonal antibodies 'down under'. *Int J Cardiol*. 2018;267:193–194.
52. Vickery AW, Bell D, Garton-Smith J, Kirke AB, Pang J, Watts GF. Optimising the detection and management of familial hypercholesterolaemia: central role of primary care and its integration with specialist services. *Heart Lung Circ*. 2014;23:1158–1164.
53. Payne J, Williams S, Maxwell D, et al. Familial hypercholesterolaemia patient support groups and advocacy: a multinational perspective. *Atherosclerosis*. 2018;277:377–382.
54. Pang J, Lansberg PJ, Watts GF. International developments in the care of familial hypercholesterolemia: where now and where to next? *J Atheroscler Thromb*. 2016;23:505–519.
55. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent hypercholesteroemia screening inprimary care. *N Engl J Med*. 2016;375:1628–1637.
56. Harada PH, Miname MH, Benseñor IM, Santos RD, Lotufo PA. Familial hypercholesterolemia prevalence in an admixed racial society: sex and race matter. The ELSA-Brasil. *Atherosclerosis*. 2018;277:273–277.
57. Steyn K, Goldberg YP, Kotze MJ, et al. Estimation of the prevalence of familial hypercholesterolaemia in a rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. *Hum Genet*. 1996;98:479–484.
58. Mabuchi H1, Nohara A, Noguchi T, et al. Molecular genetic epidemiology of homozygous familial hypercholesterolemia in the Hokuriku district of Japan. *Atherosclerosis*. 2011;214:404–407.
59. Peters DH, Tran NT, Adam T. Implementation Research in Health: a Practical Guide. Geneva, Switzerland: World Health Organization; 2013.
60. Chambers DA, Feero WG, Khoury MJ. Convergence of implementation science, precision medicine, and the learning health care system: a new model for biomedical research. *JAMA*. 2016;315:1941–1942.
61. Khoury MJ, Galea S. Will precision medicine improve population health? *JAMA*. 2016;316:1357–1358.
62. World Health Organization. Familial hypercholesterolaemia. In: Report of a Second WHO Consultation. Geneva: World Health OrganizationAvailable at: http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed April 1, 2018.