FAMILIAL HYPERCHOLESTEROLAEMIA – A GLOBAL PERSPECTIVE FROM THE EAS FAMILIAL HYPERCHOLESTEROLAEMIA STUDIES COLLABORATION (FHSC)

EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)*

* The list of authors is shown at the end of the manuscript.

Corresponding author

Dr Antonio J. Vallejo-Vaz, MD, PhD.

Department of Primary Care and Public Health, Imperial College Charing Cross campus, Reynolds Building, St Dunstan's road, W6 8RP, London, United Kingdom. +44 2075 940 778.

a.vallejo-vaz@imperial.ac.uk

Word count:

- **Abstract:** 302 words.
- **Main text:** 3,506 words.

Figures and Tables: Tables: 2; Figures: 6.

References: 21 refs.

ABSTRACT

Background. The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) global registry provides a platform for the global surveillance of FH through harmonisation and pooling of multi-national data. We characterised the adult population with heterozygous FH (HeFH) and described how HeFH is detected and managed globally.

Methods. Cross-sectional assessment of adults with a clinical and/or genetic diagnosis of probable or definite HeFH. Data were assessed overall and by WHO regions, sex, and index (IC) versus non-index cases (non-IC).

Findings. 42,167 adults (53·6% women) from 56 countries were included (79·4% diagnosed by DLCN criteria; 84·2% from Europe). Median age (interquartile range, IQR) at entry in the registry was 46·2 (34·3–58·0) years (age at FH diagnosis: 44·4 (32·5–56·5) years; 40·2% diagnosed <40 years). Prevalence of cardiovascular risk factors (CVRF) increased progressively with age and varied by WHO region. Prevalence of coronary disease was 17·4% (stroke: 2·1%, peripheral artery disease: 5·2%), increasing with LDL-C levels and ~2-fold lower in women. Of patients receiving lipid-lowering medications (LLM), 81·1% were using statins and 21·3% were on combination therapy, with greater use of more potent LLM in men versus women. Median (IQR) LDL-C among patients not taking and those taking LLM were 5·43 (4·32–6·72) and 4·23 (3·20–5·66) mmol/L. Among patients taking LLM, 2·7% had an LDL-C <1·8mmol/L; the use of combination therapy, particularly with three drugs and with PCSK9 inhibitors, associated a higher proportion and greater odds of having an LDL-C <1·8mmol/L. Non-IC, vs IC, were younger, with lower LDL-C and lower prevalence of CVRF and cardiovascular diseases (all p<0·001).

Interpretation. FH is diagnosed late. Guideline-recommended LDL-C levels are infrequently achieved with single drug therapy. CVRF and presence of coronary disease are lower among non-IC, who are diagnosed earlier. Earlier detection and greater utilisation of combination therapies are required to reduce the global burden of FH.

Study registration: ClinicalTrials.gov (NCT04272697).

Keywords

Familial hypercholesterolaemia; low-density lipoprotein cholesterol; lipid-lowering therapy; cardiovascular disease; registries: sex disparities

RESEARCH IN CONTEXT

Evidence before this study

We performed a systematic search in PubMed for research articles published from inception to February 23, 2021. Language restrictions were not applied. We included MeSH and free terms related to ("familial hypercholesterolaemia") and ("registry"/"gender"/"sex"/"index case"), or variations of these terms thereof. We screened articles by title and abstracts to identify relevant studies. Reference lists of eligible articles were also searched for additional studies. Articles that explored familial hypercholesterolaemia (FH) and registries to characterise FH and its burden, identification, and management were considered. We also reviewed the most recent guidelines and consensus statements on dyslipidaemias/FH.

Recent large meta-analyses show that FH is a relatively common inherited condition affecting ~1:300 individuals in the general population (approximately twice the prevalence historically estimated). Information on prevalence and burden of FH are lacking in many countries and regions. Low rates (<5-10%) of FH identification are consistently reported. Beyond opportunistic screening, family cascade screening and universal screening have been proposed; however, there is no consensus on the optimal strategy and screening programmes are not widely implemented, with only few exceptions. Characterisation of index versus non-index cases could help inform optimal strategies, but information reported is limited. FH increases the risk of (premature) cardiovascular disease (CVD), particularly of coronary disease, with data suggesting outcomes can be prevented through early identification and intervention. However, undertreatment is consistently reported. Sex disparities in identification and management of FH are suggested, but requires further characterisation.

Added value of this study

The Familial Hypercholesterolaemia Studies Collaboration (FHSC) provides an integrated approach to assess the global burden of FH by bringing together data from multiple sources and registries, which are standardised, harmonised and merged into a single global Registry. The study includes >42,000 heterozygous FH adults from 56 countries. Although FH occurs across all WHO regions, there are some regional variations. FH is detected late, on average in the age of 40s, with only ~40% of cases diagnosed <40 years. Prevalence of CVD and cardiovascular risk factors increase with age of diagnosis, particularly among index cases, suggesting late diagnosis potentially misses out on opportunities to address other future determinants of health in addition to LDL-C. However, for non-index cases, who appear to be diagnosed earlier, the prevalence of CVD and risk factors are lower, supporting the role of screening from index cases. Only 2.7% of treated patients achieve LDL-C <1.8mmol/L, with low use of combination therapy. Goal attainment improved incrementally with the number of therapies used,

particularly when including PCSK9 inhibitors. There are important differences by sex, with implications for screening and treatment.

Implications of all the available evidence

Identification of FH must be improved in order to detect those affected much earlier in their life-course. Greater use of combination therapy is likely required to improve FH management and reduce the gap between guideline recommendations and clinical practice; this raises challenges about accessibility and cost, particularly in low/middle-income countries. Sex disparities in FH detection and management are present, with potential implications for care and outcomes.

MAIN TEXT

Introduction

Recognition that familial hypercholesterolaemia (FH) is not an uncommon condition, whose clinical course can be improved through early detection and treatment, led to the 1998 World Health Organization (WHO) Report on FH,[1] which advocated the need to address the challenge of FH worldwide through multiple approaches. Since then, there has been limited progress in the implementation of key aspects of those recommendations, which include making an early diagnosis, providing effective treatment and raising awareness.[2] Contemporary epidemiological and genetic studies now suggest that FH is approximately twice as common as previously envisaged, potentially affecting >25 million people worldwide.[3] Yet with no consensus on approaches for detection or screening, it is estimated that <5% of those potentially affected have been diagnosed, with limited data from many world regions .[3,4]

Although different registries have been initiated in several countries to inform local policy independently, efforts to tackle the global burden of FH have been limited by the lack of an integrated approach. The European Atherosclerosis Society (EAS) FH Studies Collaboration (FHSC)[5] was established to create a global registry of FH patients, creating a network of investigators (currently from 66 countries worldwide) for the purpose of providing a platform for the global surveillance of FH through harmonisation and pooling of regional and national data. The FHSC aims to provide hitherto unavailable insights on the detection and management of FH on a global level with potential implications for future public health strategies. In the present study we specifically aimed to characterise the adult population with heterozygous FH (HeFH) and describe how HeFH is detected and managed globally.

Methods

The methods of the FHSC have been described elsewhere.[5] The FHSC draws upon data from an international consortium of investigators with access to patients managed in specialist clinics which serve as national, regional or local registries of FH. Individual data from these diverse sources are standardised to a common Data Dictionary, harmonised and merged into a single global Registry. Further details of methods and data management are described in Supplemental Methods, Supplemental Figure 1-2, and in the published protocol.[5]

The protocol and data governance of the FHSC Registry (registered at ClinicalTrials.gov NCT04272697) and its use for research have been approved by the Joint Research Compliance Office and Imperial College Research Ethics Committee, Imperial College London, United Kingdom. Investigators and organisations contributing to this registry were required to provide written

confirmation that they comply with their local research/ethical policies and regulations for sharing data with the Registry.

The FHSC Registry consists of adults and children with a clinical and/or genetic diagnosis of homozygous (HoFH) or HeFH; cases with a clinical diagnosis must conform with accepted clinical criteria (or modified criteria thereof).[4-8] Cases relying only on a self-reported history of FH and those with secondary causes of hypercholesterolaemia were excluded.

At the time of the present analysis, the FHSC Registry includes >61,600 participants. In the present study we conducted a cross-sectional assessment of adults (≥18 years) with probable or definite HeFH (possible and definite using Simon-Broome criteria) at the time individuals were entered into the registries. In cases with a clinical (non-genetic) diagnosis, we excluded those cases with untreated low-density lipoprotein-cholesterol (LDL-C) ≥12·9mmol/L (500mg/dL), since these levels make the presence of HoFH likely (either "true" HoFH or compound/double heterozygotes).[9] Data were assessed overall (global) and by WHO regions,[10] sex, and index (IC) versus non-index cases (non-IC). IC is defined as the first documented FH case in a family; non-IC are relatives with FH identified through screening of the family from the IC.

Characteristics of individual registries and cohorts contributing to the FHSC Registry are shown in Supplemental Table 1. Since the Netherlands contributed a large percentage of cases to the European region, the analysis of this region was made separately for "European region excluding the Netherlands" and "the Netherlands". Similarly, sensitivity analysis was conducted for the overall FHSC cohort excluding the Netherlands. Due to the limited number of cases from the WHO South-East Asia region, this region was considered together with the Western Pacific region.

Statistical Analysis

Merged data were analysed at individual-level on the composite dataset. Where a specific country was not granted approval by its local ethical/research committee to provide individual-level data to the FHSC (the case of French Registry of Familial Hypercholesterolaemia), similar analyses to those conducted on the merged dataset were conducted by the corresponding investigator on their own individual-level dataset, and the aggregated results were shared with the FHSC.

Descriptive estimates are presented as mean (standard deviation) or median (interquartile range, IQR), as appropriate, for continuous variables. Categorical variables are reported as absolute numbers and relative frequencies from total number of participants with data available for the corresponding variable. No attempt was made to account for missing variables due to the descriptive nature of the analysis; data available for the variables included in the study are shown in Supplemental Table 2. Between-group comparisons of continuous variables were conducted using independent-samples T test or Mann-Whitney U test for normally and non-normally distributed variables, respectively; Chi-squared test was

used for categorical variables. Where appropriate, odds ratios (ORs) and 95% confidence intervals (95%CI) were estimated using logistic regression to assess the association between a condition of interest and a certain exposure adjusting by relevant variables. Tests were 2-sided; statistical significance was defined as $p<0{\cdot}05$. The analyses were performed using IBM SPSS Statistics.

Role of the Funding Source

The funders did not have any role in: study design; conducting the study; data collection, analysis, and interpretation; writing/reviewing the manuscript; decision to submit for publication.

Results

A total of 42,167 adults with HeFH from 56 countries were included in the present analysis, Supplemental Figure 2. Most cases (79·4%) were diagnosed using the DLCN criteria (either clinical criteria only, or both clinical and genetic criteria); Simon-Broome criteria was used in 1·6% of cases; MEDPED, in 6·7%; genetic criteria only, in 10·5%; and other diagnostic system in 1·8% (Supplemental Table 1). Most cases came from the European region: 84·2%, including 46·3% from the Netherlands (Table 1). For the African region, 99·4% of cases arose from South Africa (remainder from Nigeria).

Table 1 shows the characteristics of participants at entry in the registry. Median age was 46·2 years and 53·6% were women. Age at which FH was diagnosed was known in 30,560 participants and was a median of 44·4 years (Table 1) (40·2% diagnosed <40 years; 2·1% diagnosed <18 years; Figure 1, Supplemental Figure 3). Prevalence of hypertension and diabetes were 19·2% and 5·0%, respectively; 50·1% of patients had a body mass index (BMI) $\geq 25 kg/m^2$; the prevalence of CVRF increased progressively with age (Figure 2; Supplemental Figure 4) and varied by region (Table 1). There was a higher prevalence of hypertension in Europe (excluding Netherlands), and a higher prevalence of diabetes and higher BMI in the Eastern Mediterranean region. By comparison, a lower prevalence of these CVRF was observed in the Dutch cohort.

Coronary artery disease (CAD) was the most prevalent type of cardiovascular disease (CVD) (17·4%, versus stroke: 2·1% and peripheral artery disease [PAD]: 5·2%), Table 1. Prevalence of premature CAD (<55/60 years in men/women) was 11·3%. The prevalence of CAD increased progressively with increasing levels of untreated LDL-C ($p<0{\cdot}0001$), unlike stroke and PAD where prevalences did not vary significantly across LDL-C levels (both $p\geq 0{\cdot}33$); Figure 3. The Dutch cohort had lower prevalences of CAD and stroke (Table 1).

Table 2 shows the characteristics of participants by sex. Women were, on average, ~2·5 years older than men at the time of FH diagnosis, with 38·4% diagnosed <40 years of age, versus 42·3% of men (Figure

1). Prevalence of CAD was ~2-fold lower in women versus men (p<0·0001) (Figure 4.A). After adjusting for age, baseline characteristics, lipid levels and LLM, women had a significantly lower odds of having CAD than men (Figure 4.B). There were no significant differences by sex in the prevalence of stroke or PAD (Figure 4; Supplemental Table 4).

At the time of study entry, 59·5% of patients were taking LLM (Figure 5; Supplemental Table 5). Among patients on LLM, 81·1% were taking statins, with or without other LLM (Figure 5.A; Supplemental Table 6). These percentages were similar for men (81·2%) and women (80·9%), p=0·60, Supplemental Figure 5; however, more men (16·6%) than women (13·1%) were on the highest statin doses (atorvastatin 80mg/day or rosuvastatin 40mg/day), p<0·001 (Supplemental Table 7). The proportion of men, versus women, taking ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) (with/without any other LLM) were 25.9%, versus 23.4%, and 3.5%, versus 2.5%, respectively; both p≤0·0002 (Supplemental Figure 5). Overall, considering LLM with statins, ezetimibe or PCSK9i, 21·3% of patients were on combination therapy (men: 22·7%, women: 19·9%, p<0·0001) (Figure 5.B; Supplemental Figure 5; Supplemental Table 8).

Lipid levels, stratified by those taking/not taking LLM, are shown in Table 1 and Supplemental Table 9. LDL-C was broadly similar between men and women when considering the overall cohort (Table 2); however, when stratified by age of 50 (broadly accounting for pre-/post-menopause in women), LDL-C among those not on LLM were significantly higher among women ≥50 years old compared to men above the same age (median 5·93 [IQR 4·86–7·17] versus 5·20 [4·19–6·40] mmol/L, respectively; mean difference 0·64mmol/L [95%CI 0·46, 0·82], p<0·0001); there were no significant differences in LDL-C by sex below age 50 years, p=0·31 (Supplemental Table 10). Differences in LLM and prevalence of CVD in women by age of 50 are shown in Supplemental Table 11.

Among patients taking LLM (specifically statins, ezetimibe and/or PCSK9i), 2·7% had an LDL-C <1.8mmol/L at entry in the registry (Figure 6.A); this percentage was lower for women (2·0%, versus men: 3·4%, p<0·0001) (Supplemental Figure 6.A). After adjusting for age, baseline characteristics and type of LLM, the odds of having an LDL-C <1.8mmol/L were lower for women compared with men (OR 0·63, 95%CI 0·48, 0·82; p=0·0007) (Supplemental Figure 6.B). The use of combination therapy was associated with a higher proportion and greater odds of having an LDL-C <1.8mmol/L, particularly with the combination of three drugs and when using PCSK9i (Figures 6.B-D). Similar patterns were observed for LDL-C goal <1.4mmol/L (Supplemental Figure 7).

The results for the overall cohort stratified by IC/non-IC are shown in Table 2 and Figure 4.C-D. Non-IC were younger at diagnosis, with lower prevalence of hypertension and diabetes, and lower BMI, though they were more frequently smokers than IC. Untreated LDL-C was ~1·55mmol/L lower in non-IC versus IC (p<0·0001; Table 2). Prevalence of CAD and PAD were lower among non-IC compared

with IC (all p<0·0001), with no detectable difference in stroke (p=0·42) (Figure 4.C; Supplemental Table 12). A similar pattern remained when the results were stratified by both IC/non-IC and sex (Supplemental Figure 8). After adjusting for differences including age, sex, CVRF, lipid levels and LLM, non-IC had lower odds of having CVD compared with IC, mostly reflected by lower odds of CAD (Figure 4.D). The Netherlands accounted for the majority of the non-IC cohort; therefore, this cohort were further separated into "Non-IC cohort excluding the Netherlands" and "The Netherlands" (Supplemental Table 13).

Discussion

Registries are a valuable tool to help assess current practices, monitor patients, identify gaps in care including guideline implementation, and ultimately inform policy.[2] While FH registries are available in many countries aimed at research or to audit quality standards, there is no integrated approach globally. Variability in such segregated approaches has complicated efforts to harmonise and integrate information from diverse sources, impeding reliable comparisons across, for instance, different regions/countries to quantify current practices, assess geographical differences in care and, thereby, inform global public health policy regarding FH.[5] Through standardisation of nomenclature (FHSC Data Dictionary), creating a bespoke platform for data entry, and harmonisation, the FHSC attempts to overcome these limitations to provide a global perspective of FH detection and care.

The present study, the first to report from the FHSC Registry, not only confirms and reinforces findings found in local registries but also provides novel results and expands the findings to include countries that are usually underrepresented in the literature. Our results show that FH occurs across all WHO regions. Regional variations were observed which could reflect, among other factors, population characteristics, time and method of diagnosis, or differences in detection programmes. Despite FH being a common condition,[3,11] identification of cases seems to be low, particularly outside Western countries. Mean age of diagnosis globally was 43 and 46 years in men and women respectively, with less than half of adult cases diagnosed <40 years of age, and only 2% diagnosed before the age of 18. For a genetic condition leading to (if untreated) lifelong exposure to elevated LDL-C, these data mean diagnoses and ultimately therapeutic interventions, occur too late. It may reflect, among other factors, a lack of early screening programmes.[12] Detection globally tends to rely on finding IC, opportunistic screening such as health checks, or investigation of isolated findings of an elevated LDL-C measurement. Where some form of cascade testing (formal or otherwise) identified non-IC, identification appeared to be made several years earlier, with presence of fewer CVRF and lower prevalence of CVD.

In addition to the acknowledged impact of FH on cardiovascular risk, patients with FH are likely to also be harmed by other CVRF, which may contribute to further increase their cardiovascular risk.[13] In this regard, although the overall prevalence of hypertension was found to be 19·2% and diabetes 5·0%, these varied by region and both were more common with increasing age. These data highlight that, whilst FH occurs globally and there are common goals directed at detection and care, behaviour and cultural aspects may need to be considered in guiding regional health policy, accounting among others for the impact of other CVRF on overall cardiovascular risk. Although most FH cases were detected after the age of 40, we observed that the prevalence of hypertension was only 3·5% and diabetes 1·1% among those <40 years of age, underscoring the potential opportunities afforded through early diagnosis of FH. This could facilitate the need for healthy lifestyles early to reduce risk of developing additional CVRF later in life.

The commonest manifestation of CVD was CAD with many events occurring prematurely. Although there was a graded relationship between LDL-C levels and prevalence of CAD, there was no similar trend for either PAD or stroke. These findings reinforce the opportunity among those with premature CAD to detect IC as a means to initiate cascade testing.[13,14] This concept is supported by our observation that among non-IC, the prevalence of CAD and premature CAD were about one-half and one-third of IC, respectively, underscoring the importance of early detection, particularly if performed systematically like in the Netherlands. In the absence of a graded relationship between LDL-C and vascular diseases other than CAD, further work is needed to determine how FH might be part of a differential diagnosis among those with PAD or stroke. These observations are in agreement with prior reports suggesting that cardiovascular manifestations of FH are mainly related to CAD and to a lesser extent, to PAD, whereas the association of FH with stroke remains more controversial.[3,15-17]

The present study highlights sex disparities in FH. Although women had broadly similar untreated LDL-C and prevalence of CVRF, the prevalence of CAD and premature CAD was half that observed in men, even though the average age of FH diagnosis occurred later in women. In contrast, no clear differences in prevalence of stroke or PAD were observed. As clinical criteria for diagnosis usually include a personal history of premature vascular disease,[4,6] cases of FH in women, based on our findings, would be more reliant on other characteristics such as physical examination findings or absolute LDL-C. Whether the present scoring systems should be refined with sex-specific criteria is a hypothesis worth investigating to avoid sex disparities in case detection. Sex differences were further observed for therapy, with women less likely to receive higher potency lipid-lowering regimens, and less likely to achieve LDL-C goals. Perceived concerns in treating women of childbearing potential may be one factor contributing to sex-related and within women (pre/post-menopause) differences in LLM.

Globally individuals with FH are managed mostly by monotherapy with statins (though only ~14% were receiving the highest doses of atorvastatin or rosuvastatin). Combination therapy of statins with

ezetimibe or triple therapy with PCSK9i increases the likelihood of LDL-C goal attainment. Most guidelines recommend LDL-C <1.8mmol/L or lower for patients with FH,[18,19] yet in the present study only 2·7% of treated patients at entry in the registry had LDL-C levels below that figure. Goal attainment improved incrementally with the number of therapies used, with our data suggesting that if the gap between guideline recommendations and clinical practice is to be reduced, greater use of combination and, in particular, PCSK9i, are likely to be needed. This raises challenges about accessibility and cost, particularly in low- and middle-income countries.

The cohort from the Netherlands represents a large proportion of cases in this Registry. Therefore, we conducted sensitivity analysis for the overall cohort excluding the Netherlands, and the Netherlands only. In addition, the Netherlands cohort results from a large, nationwide, publicly funded, cascade screening programme, which ran for about 20 years,[20,21] leading to the identification of many non-IC. This gave us the opportunity to compare this type of programme with the rest of the FHSC cohort, which mostly relies on case-finding, opportunistic screening and limited cascade screening in some cases. The participants from the Netherlands (overall and non-IC) were, on average, younger, with lower prevalences of CVRF (except smoking –higher in the Dutch cohort, likely related to this cohort running during the 1990s) and CVD, and had lower untreated LDL-C. These data reinforce the value of wide screening programmes, supported by appropriate policies and resources, to identify larger numbers of FH cases and to do so earlier and when patients are "healthier", which will ultimately impact CVD prevention.

Limitations

The limitations of the present study merit consideration. The probability of being included in one of these registers depends on numerous factors. One of the most critical is the local health system and the processes in place to detect and diagnose cases, including the extent to which cascade testing is used. Although the sites participating in the FHSC are major lipid clinics in each of the participating sites, there may be patients with FH being managed within the same clinics that are not placed onto a local register. Those patients with symptomatic vascular disease are more likely to be diagnosed sooner than those without symptoms. Likewise, systematic factors outside of the intrinsic pathological processes may influence the relative likelihood of diagnosis being made based on age and sex. It may well be that, at least in some settings, a patient is more likely to be diagnosed with FH if for instance local or national care pathways ask primary healthcare providers to refer to specialist clinics such as the ones recruiting into the FHSC, when LDL-C or cholesterol levels exceed certain thresholds. Data within the FHSC Registry come from different sources.[12] While data sources have broadly similar inclusion/exclusion criteria and standardised information (utilising a common data dictionary), variability in the data source (e.g. different specialist clinics, several diagnostic criteria systems) provides some heterogeneity within the data. The representation of cases from certain WHO regions is limited. Moving forward, global

collaboration can be further enhanced through expansion of the FHSC Registry to include data from countries yet to participate, through either provision of individual data or summary data analogous to the French registry. Where genetic testing was not available/accessible, a clinical diagnosis was made; therefore, the possibility that some cases without a molecular diagnosis, particularly among those with milder phenotypes, may have an alternative aetiology resembling an FH phenotype (e.g. polygenic hypercholesterolaemia); to limit this from happening, where clinical criteria were applied only patients with probable or definite FH were included in the study. Registries are observational by nature and some variables were not captured in all countries. While we have statistically adjusted for different variables where appropriate, the presence of potential confounders cannot be fully ruled out for subgroup comparisons. Patients with severest phenotypes may have died before they could have been captured in the local registries (potential survival bias). Most local registries are centred in specialist clinics, with some specialisation in lipids, which may imply that gaps in care identified in this study could be more pronounced in general practice or in other non-specialised clinics. Finally, regarding LLM, given present analyses are at the time of entry in the registry (which in some cases is when the patients are first identified with FH or when they are first referred to a specialist clinic) the treatment may have not yet been intensified. The fact that many patients were included in the respective national/local registries some years ago, before PCSK9i were available, may partly account for the low percentage of patients taking this medication.

Conclusions

This report from the FHSC reveals that FH is diagnosed late and control of LDL-C levels fall far below guideline recommendations in part because of pharmacological monotherapy-based regimens. Earlier, more systematic detection of FH and greater use of combination therapy will be required to improve FH care globally.

*** List of Authors**

Dr Antonio J. Vallejo-Vaz[1], PhD, Mr Christophe A.T. Stevens[1], MSc, Dr Alexander R.M. Lyons[1], PhD, Ms Kanika I. Dharmayat[1], MPH, Prof Tomas Freiberger[2], MD, Prof G. Kees Hovingh[3], MD, Prof Pedro Mata[4], MD, Prof Frederick J. Raal[5], PhD, Prof Raul D. Santos[6], PhD, Dr Handrean Soran[7], MD, Prof Gerald F. Watts[8,9], DSc, Prof Marianne Abifadel[10], PhD, Dr Carlos A. Aguilar-Salinas[11,12], PhD, Dr Khalid F. Alhabib[13], MBBS, Dr Mutaz Alkhnifsawi[14], MD, Dr Wael Almahmeed[15], FRCPC, Dr Fahad Alnouri[16], MD, Dr Rodrigo Alonso[17], PhD, Prof Khalid Al-Rasadi[18,19], MD, Dr Ahmad Al-Sarraf[20], MD, Dr Nasreen Al-Sayed[21], MD, Dr Francisco Araujo[22], MD, Dr Tester F. Ashavaid[23], PhD, Prof Maciej Banach[24-26], PhD, Dr Sophie Béliard[27], MD, Prof Marianne Benn[28], DMSc, Prof Christoph J. Binder[29], MD, Prof Martin P. Bogsrud[30], PhD, Prof Mafalda Bourbon[31,32], PhD, Dr Krzysztof Chlebus[33], PhD, Dr Pablo Corral[34], MD, Prof Kairat Davletov[35], PhD, Prof Olivier S. Descamps[36], PhD, Prof Ronen Durst[37], MD, Dr Marat Ezhov[38], DMSc, Prof Dan Gaita[39], FESC, Prof Jacques Genest[40], MD, Dr Urh Groselj[41,42], MD, Prof Mariko Harada-Shiba[43], MD, Prof Kirsten B. Holven[30], PhD, Prof Meral Kayikcioglu[44], MD, Prof Weerapan Khovidhunkit[45], MD, Prof Katarina Lalic[46], PhD, Prof Gustavs Latkovskis[47], PhD, Prof Ulrich Laufs[48], MD, Dr Evangelos Liberopoulos[49], MD, Dr Marcos M. Lima-Martinez[50], MD, Dr Jie Lin[51], PhD, Dr Vincent Maher[52], MD, Prof A. David Marais[53], MBChB, Prof Winfried März[54-57], MD, Prof Erkin Mirrakhimov[58], MD, Prof André R. Miserez[59,60], MD, Prof Olena Mitchenko[61], MD, Prof Hapizah Nawawi[62], FRCP, Prof Børge G. Nordestgaard[63], DMSc, Dr Andrie G. Panayiotou[64], PhD, Prof György Paragh[65], DSc, Prof Zaneta Petrulioniene[66], PhD, Prof Belma Pojskic[67], PhD, Prof Arman Postadzhiyan[68], MD, Dr Katarina Raslova[69], MD, Dr Ashraf Reda[70], MD, Prof Željko Reiner[71], MD, Dr Fouzia Sadiq[72], PhD, Dr Wilson Ehidiamen Sadoh[73], MPH, Prof Heribert Schunkert[74,75], MD, Dr Aleksandr B. Shek[76], MD, Dr Mario Stoll[77], MD, Dr Erik Stroes[3], MD, Dr Ta-Chen Su[78], PhD, Dr Tavintharan Subramaniam[79], FRCP, Prof Andrey V. Susekov[80], MD, Dr Myra Tilney[81,82], FRCP, Dr Brian Tomlinson[83], MD, Dr Thanh Huong Truong[84], PhD, Prof Alexandros D. Tselepis[85], PhD, Prof Anne Tybjærg-Hansen[28], DMSc, Dr Alejandra Vázquez Cárdenas[86], PhD, Dr Margus Viigimaa[87], MD, Prof. Luya Wang[88], MD, Prof Shizuya Yamashita[89], MD, Prof Lale Tokgozoglu[90], MD, Prof Alberico L. Catapano[91,92], PhD, Prof Kausik K. Ray[1], FRCP; on behalf of the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) Investigators**.

** EAS FHSC Committees and Investigators are listed in the Appendix (Supplemental Material).

Affiliations

1- Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, School of Public Health, Imperial College London. London, United Kingdom.

2- Centre for Cardiovascular Surgery and Transplantation, Brno, Czech Republic; and Medical Faculty, Masaryk University, Brno, Czech Republic.

3- Dept of vascular medicine, Academic Medical Centre, Amsterdam, The Netherlands.

4- Fundación Hipercolesterolemia Familiar, Madrid, Spain.

5- Carbohydrate and Lipid Metabolism Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

6- Heart Institute (InCor) University of Sao Paulo and Hospital Israelita Albert Einstein, Sao Paulo, Brazil.

7- Manchester University NHS Foundation Trust, Manchester, UK.

8- School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Australia.

9- Lipid Disorders Clinic, Cardiometabolic Services, Department of Cardiology, Royal Perth Hospital, Perth, Australia.

10- Laboratory of Biochemistry and Molecular Therapeutics, Faculty of Pharmacy, Saint Joseph University, Beirut, Lebanon.

11- Unidad de Investigación de Enfermedades Metabólicas, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, México.

12- Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, México.

13- Department of Cardiac Sciences, King Fahad Cardiac Centre, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

14- Faculty of Medicine, University of Al Qadisiyah, Iraq.

15- Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, United Arab Emirates.

16- Cardiovascular Prevention Unit, Adult Cardiology Department, Prince Sultan Cardiac Centre Riyadh, Saudi Arabia.

17- Center for Advanced Metabolic Medicine and Nutrition, Santiago.

18- Medical research Centre, Sultan Qaboos University, Muscat, Oman.

19- Department of Biochemistry, College of Medicine & Health Science, Sultan Qaboos University, Muscat, Oman.

20- Sabah Al Ahmad Cardiac Centre, Kuwait.

21- Gulf Diabetes and Endocrine Centre, Bahrain.

22- Portuguese Atherosclerosis Society, Portugal.

23- P.D. Hinduja Hospital and Medical Research Centre, Mahim, Mumbai, India.

24- Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland.

25- Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland.

26- Cardiovascular Research Centre, University of Zielona Gora, Zielona Gora, Poland.

27- APHM, Hôpital de la Conception and Centre de Recherche en Cardiovasculaire et Nutrition C2VN, UMR 1263 INSERM 1260 INRAE Aix Marseille Université, Marseille, France.

28- Department of Clinical Biochemistry, Rigshospitalet, Copenhagen, Denmark; and Department of Clinical Medicine, Faculty of Health and medical Sciences, University of Copenhagen, Denmark.

29- Department of Laboratory Medicine, Medical University of Vienna, Austria.

30- National Advisory Unit on FH, Oslo University Hospital, Norway.

31- Unidade de I&D, Grupo de Investigação Cardiovascular, Departamento de Promoção da Saúde e Prevenção de Doenças Não Transmissíveis, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisboa, Portugal.

32- BioISI – Biosystems & Integrative Sciences Institute, Faculty of Sciences, University of Lisboa, Lisboa, Portugal.

33- 1st Department of Cardiology Medical University of Gdansk, National Centre of Familial Hypercholesterolaemia in Gdańsk, Poland.

34- FASTA University, School of Medicine, Pharmacology Department, Mar del Plata, Argentina.

35- Research Health Institute, Al Farabi Kazakh National University, Almaty, Kazakhstan.

36- Centre de Recherche Médicale de Jolimont, Centres hospitaliers Jolimont, Belgium.

37- Cardiology Department and Centre for Treatment and Prevention of Atherosclerosis, Hadassah Hebrew University Medical Centre, Jerusalem, Israel.

38- National Medical Research Centre of Cardiology of Ministry of Health of the Russian Federation, Moscow, Russia.

39- Universitatea de Medicina si Farmacie Victor Babes, Institutul de Boli Cardiovasculare, Fundatia CardioPrevent, Timisoara, Romania.

40- McGill University, Canada.

41- Department of Pediatric Endocrinology, Diabetes and Metabolism, UMC – University Children's Hospital Ljubljana, Slovenia.

42- University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia.

43- National Cerebral and Cardiovascular Centre Research Institute, Japan.

44- Ege University Medical School Department of Cardiology, Turkey.

45- Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thailand.

46- Faculty of Medicine University of Belgrade, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Belgrade, Serbia.

47- Research Institute of Cardiology and Regenerative Medicine, Faculty of Medicine, University of Latvia, Pauls Stradins Clinical University Hospital, Riga, Latvia.

48- Klinik und Poliklinik für Kardiologie, Universitätsklinikum Leipzig, Leipzig, Germany.

49- Department of Internal Medicine, Faculty of Medicine, University of Ioannina, Ioannina, Greece.

50- Universidad de Oriente, Nucleo Bolivar, Venezuela.

51- Beijing Anzhen Hospital Capital Medical University, Beijing Institute of Heart Lung & Blood Vessel Diseases, China.

52- Advanced Lipid Management and Research Centre A.L.M.A.R. Tallaght University Hospital, Dublin, Ireland.

53- Chemical Pathology, University of Cape Town Health Science Faculty, South Africa.

54- DACH Society for the Prevention of Heart and Circulatory Diseases (registered society), Hamburg, Germany.

55- Department of Internal Medicine V Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

56- Klinisches Institut für Medizinische und Chemische Labordiagnostik, Medizinische Universität Graz, Graz, Austria.

57- Synlab Akademie, Synlab Holding Deutschland GmbH, Mannheim und Augsburg, Germany.

58- Kyrgyz State Medical Academy, Bishkek, Kyrgyzstan.

59- diagene Research Institute, Reinach, Switzerland; Faculty of Medicine, University of Basel, Basel, Switzerland.

60- Swiss Society for Familial Forms of Hypercholesterolemia (SSFH), Reinach, Switzerland.

61- Dyslipidaemia department, Institute of cardiology AMS, Ukraine.

62- Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM) and Faculty of Medicine, Universiti Teknologi MARA (UiTM), Sungai Buloh, Selangor, Malaysia.

63- Herlev and Gentofte Hospital, Copenhagen University Hospital, University of Copenhagen, Denmark.

64- Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Cyprus.

65- Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary.

66- Vilnius University Faculty of Medicine, Vilnius, Lithuania; Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania.

67- Cantonal Hospital Zenica, Bosnia and Herzegovina.

68- Medical University of Sofia, Bulgaria.

69- Coordination Centre for Familial Hyperlipidemias, Slovak Medical University in Bratislava, Slovakia.

70- Menofeya University, Faculty of medicine, Cardiology department, Egypt.

71- Department of Internal medicine, University Hospital Centre Zagreb, School of Medicine University of Zagreb, Croatia.

72- Directorate of Research, Shifa Tameer-e-Millat University, Pakistan.

73- Department of Child Health, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria.

74- Clinic for Heart and Circulatory Diseases, German Heart Centre Munich, Technical University Munich, Munich, Germany.

75- DZHK (German Centre for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany.

76- CAD and Atherosclerosis Department, Republican Specialized Centre of Cardiology (RSCC), Ministry of Health of Republic Uzbekistan, Tashkent, Uzbekistan.

77- GENYCO Program, Comisión Nacional de Salud Cardiovascular, Uruguay.

78- Departments of Internal Medicine and Environmental and Occupational Medicine, National Taiwan University Hospital, Taiwan.

79- Admiralty Medical Centre and Khoo Teck Puat Hospital, Yishun Health, Singapore.

80- Academy for Postgraduate Medical Education, Faculty of Clinical Pharmacology and therapeutics, Ministry of Health, Moscow, Russian Federation.

81- Lipid Clinic, Mater Dei Hospital, Malta.

82- Department of Medicine, Faculty of Medicine and Surgery, University of Malta, Malta.

83- Faculty of Medicine, Macau University of Science and Technology, Macau, China.

84- Vietnam National Heart Institute, Bach Mai Hospital; Department of Cardiology, Hanoi Medical University, Vietnam.

85- Atherothrombosis Research Centre, University of Ioannina, Greece.

86- Facultad de Medicina, Universidad Autónoma de Guadalajara, Mexico.

87- North Estonia Medical Centre, Tallinn University of Technology, Estonia.

88- Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, China.

89- Rinku General Medical Centre, Japan.

90- Hacettepe University, Ankara, Turkey.

91- Centre of Epidemiology and Preventive Pharmacology, Laboratory of Lipoproteins, Immunity and Atherosclerosis, Department of Pharmacological and Biomolecular Sciences University of Milan, Italy.

92- I.R.C.C.S. MultiMedica, Milan, Italy.

Authors' contribution

Dr AJ Vallejo-Vaz, Mr CAT Stevens, Ms KI Dharmayat, Prof T Freiberger, Prof GK Hovingh, Prof JJP Kastelein, Prof P Mata, Prof FJ Raal, Prof RD Santos, Dr H Soran, Prof GF Watts, Prof AL Catapano and Prof KK Ray contributed to the conception and design of the work. All authors contributed to the acquisition and/or interpretation of data for the work. Dr AJ Vallejo-Vaz, Mr CAT Stevens and Ms KI Dharmayat conducted the analysis. Dr AJ Vallejo-Vaz and Prof KK Ray drafted the manuscript. All authors critically revised the manuscript and gave final approval.

Declaration of Interests

Authors listed alphabetically by last name. **CAAS** reports grants from Amgen, during the conduct of the study. **MA** has nothing to disclose. **KA** has nothing to disclose. **MA** has nothing to disclose. **WA** has nothing to disclose. **FA** reports grants from National Science, Technology and Innovation Plan, Kingdom of Saudi Arabia, during the conduct of the study; personal fees from Amgen, Amryt Pharma,

Algorithma Pharma, outside the submitted work. **RA** reports personal fees and non-financial support from tecnofarma, Novonordisk, Abbott, Saval, Teva, outside the submitted work. **KAR** reports personal fees from Sanofi, Abbott, outside the submitted work. **AAS** has nothing to disclose. **NAS** reports personal fees from Sanofi, Amgen, Merck, AstraZeneca, outside the submitted work. **FA** has nothing to disclose. **TFA** has nothing to disclose. **MB** reports grants, personal fees, non-financial support and other from Akcea, Amgen, Daiichi-Sankyo, Esperion, Freia Pharmaceuticals, Herbapol, Kogen, KRKA, Mylan, Novartis, Novo-Nordisk, Polfarmex, Polpharma, Resverlogix, Sanofi-Regeneron, Servier, Teva, Valeant, and Zentiva, during the conduct of the study. **SB** reports grants from ANR (government), grants from Amgen, Sanofi, during the conduct of the study. **MB** has nothing to disclose. **CJB** reports grants from Amgen, Sanofi, Alexion, during the conduct of the study; personal fees from Akcea, Novartis, Amgen, outside the submitted work. **MPB** reports personal fees from Amgen, Sanofi, outside the submitted work. **MB** reports grants from Science and Technology Foundation, Akcea, during the conduct of the study; grants from Science and Technology Foundation, Akcea, outside the submitted work. **AVC** has nothing to disclose. **ALC** has received honoraria, lecture fees, or research grants from Akcea, Amgen, AstraZeneca, Eli Lilly, Genzyme, Kowa, Mediolanum, Menarini, Merck, Pfizer, Recordati, Sanofi, Sigma Tau, Medco, Amryt. **KC** has nothing to disclose. **PC** reports grants and personal fees from Amgen, PTC Therapeutics, Novartis, AstraZeneca, outside the submitted work. **KD** has nothing to disclose. **OSD** reports grants and personal fees from Amgen, Sanofi, MSD, Daichii Sankyo, Novartis, outside the submitted work. **KID** reports grants from Pfizer, Amgen, MSD, Sanofi-Aventis, Daichii-Sankyo, Regeneron, during the conduct of the study; personal fees from Bayer, outside the submitted work. **RD** has nothing to disclose. **ME** has nothing to disclose. **TF** reports grants from Ministry of Health, CR, during the conduct of the study; personal fees from Novartis, Sanofi, Amgen, outside the submitted work. **DG** has nothing to disclose. **JG** reports grants from Canadian Institutes of Health Research, during the conduct of the study. **UG** has nothing to disclose. **ATH** reports personal fees from AstraZeneca, Sanofi, Regeneron, Akcea, Novartis, Silence Therpeutics, Draupnir Bio, outside the submitted work. **MHS** reports grants and personal fees from Japanese Ministry of Health, Labour and Welfare, Japanese Circulation Society, Astellas Pharm, Takeda, MSD, Kaneka Medics, Aegerion, Recordati, Sanofi, Kowa, Daiichi-Sankyo, Mochida, outside the submitted work. **KBH** reports grants and personal fees from Mills SA, Tine DA, Amgen, Sanofi, Null, outside the submitted work. **GKH** reports grants from Kowa Research Europe, during the conduct of the study; research grants from the Netherlands Organization for Scientific Research (VIDI), Klinkerpad fonds, and the European Union; institutional research support from Aegerion, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis, Kowa, Pfizer, Regeneron, Roche, Sanofi, and The Medicines Company; speaker's bureau and consulting fees from Amgen, Aegerion, Sanofi, and Regeneron Pharmaceuticals; part-time employed by Novo Nordisk A/S. **MK** reports grants and personal fees from Abbott, Actelion, AstraZeneca, Abdi Ibrahim, Aegerion, Bayer Schering, Menarini, Sanofi Genzyme, Pfizer, Aegerion, Amyrt Pharma, Amgen, Sanofi, outside the submitted work. **WK** reports grants from The Royal College of Physicians of Thailand, The

Endocrine Society of Thailand, during the conduct of the study; grants and other from Amgen, outside the submitted work. **KL** has nothing to disclose. **GL** reports grants, personal fees and non-financial support from Latvian National Research Program Biomedicine for Public Health (Biomedicine) 2014–2017, the Ministry of Education and Science of the Republic of Latvia, grants, personal fees and non-financial support from Latvian Science Council, project Nr. lzp-2020/1-0151, Amgen, Pfizer, AstraZeneca, Servier, Sanofi, Mylan, Novartis, MSD, KRKA, Zentiva, during the conduct of the study; personal fees and non-financial support from Bayer, Boehringer Ingelheim, Grindex, Medtronic, Abbott Laboratories, Siemens Laboratories, Novo Nordisk, outside the submitted work. **UL** has nothing to disclose. **EL** reports personal fees and non-financial support from Hellenic Atherosclerosis Society, during the conduct of the study; personal fees from Amgen, Novartis, Mylan, Servier, outside the submitted work. **MMLM** has nothing to disclose. **JL** has nothing to disclose. **ARML** reports grants from Pfizer, Amgen, MSD, Sanofi-Aventis, Daichii-Sankyo, Regeneron, during the conduct of the study. **VM** has nothing to disclose. **DM** has nothing to disclose. **WM** reports grants and personal fees from Siemens Healthineers, Aegerion Pharmaceuticals, Amgen, AstraZeneca, Sanofi, Amryt Pharmaceuticals, BASF, Abbott Diagnostics, Numares AG, Berlin-Chemie, Akzea Therapeutics, Bayer Vital GmbH, Bestbion dx GmbH, Boehringer Ingelheim Pharma GmbH Co KG, Immundiagnostik GmbH, Merck Chemicals GmbH, Novartis Pharma GmbH, Olink Proteomics, Amgen, Novartis Pharma, Vifor Pharma, other from SYNLAB Holding Deutschland GmbH, outside the submitted work. **PM** has nothing to disclose. **EM** has nothing to disclose. **ARM** has nothing to disclose. **OM** has nothing to disclose. **HN** reports grants from Malaysian Ministry of Higher Education, FH-10countries, Univ Western Australia/ FH Australasian Network/APSAVD, BioEazy Sdn Bhd, non-financial support from European Atherosclerosis Society, during the conduct of the study. **BGN** reports personal fees from AstraZeneca, Sanofi, Regeneron, Akcea, Amgen, Kowa, Denka Seiken, Amarin, Novartis, Novo Nordisk, Esperion, Silence Therap, outside the submitted work. **AP** has nothing to disclose. **GP** has nothing to disclose. **ZP** has nothing to disclose. **BP** has nothing to disclose. **AP** has nothing to disclose. **FJR** reports personal fees from Amgen, Sanofi-Aventis, Regeneron, Novartis, outside the submitted work. **KR** has nothing to disclose. **KKR** reports grants and personal fees from Amgen, Sanofi/ Regeneron, Pfizer, AstraZeneca, Medicines Company, Kowa, Novartis, Lilly, Algorithm, Boehringer Ingelheim, MSD, Abbvie, Silence Therapeutics, Bayer, Daiichi Sankyo, Esperion, Abbott, New Amsterdam, Resverlogix, outside the submitted work. **AR** has nothing to disclose. **ŽR** reports personal fees from Sanofi, Novartis, outside the submitted work. **FS** has nothing to disclose. **WES** has nothing to disclose. **RDS** reports grants and personal fees from Abbott, Amgen, AstraZeneca, Akcea, Biolab, Esperion, EMS, Kowa, Libbs, GETZ Pharma, MSD, Merck, Novartis, Novo-Nordisk, PTC Therapeutics, Pfizer, Sanofi/Regeneron, outside the submitted work. **HS** reports personal fees from MSD Sharp & Dohme, Amgen, Bayer Vital GmbH, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, Servier, Brahms, Bristol-Myers Squibb, Medtronic, Sanofi Aventis, Synlab, AstraZeneca, Pfizer, Vifor, outside the submitted work. **ABS** has nothing to disclose. **HS** has nothing to disclose. **CATS** reports

grants from Pfizer, Amgen, MSD, Sanofi-Aventis, Daichii-Sankyo, Regeneron, during the conduct of the study. **MS** has nothing to disclose. **ES** reports personal fees from Amgen, Sanofi-Regeneron, Esperion, Novartis, Novo-Nordisk, outside the submitted work. **TCS** has nothing to disclose. **TS** has nothing to disclose. **AVS** reports Lecturer, honoraria from AstraZeneca, Abbott, KRKA, Teva Pharmaceuticals, Sanofi, Amgen, Servier, Akrichin, Janssen. **MT** reports personal fees from Sanofi, outside the submitted work. **LT** reports personal fees from Abbott, Amgen, Mylan, Sanofi, Novartis, Recordati, Daiichi-Sankyo, Pfizer, outside the submitted work. **BT** reports personal fees from Amgen, KOWA, MERCK SERONO, outside the submitted work. **TH** has nothing to disclose. **AT** reports grants and personal fees from AstraZeneca, Elpen, Libytec, Epsilon Health, Galenica SA, outside the submitted work. **AJVV** reports participation in research grants to the European Atherosclerosis Society/Imperial College London from Pfizer, Amgen, MSD, Sanofi-Aventis, Daichii-Sankyo and Regeneron, during the conduct of the study; personal fees for consulting from Bayer and honoraria for lectures from Amgen, Mylan, Akcea, outside the submitted work. **MV** has nothing to disclose. **LW** has nothing to disclose. **GFW** reports grants and personal fees from Amgen, Regeneron, Sanofi, Novartis, Arrowhead, AstraZeneca, Kowa, Esperion, outside the submitted work. **SY** reports personal fees from Kowa Company Ltd., MSD K.K., Skylight Biotec Inc., Hayashibara Co., Ltd., Recordati Rare Diseases Japan K.K., outside the submitted work.

Acknowledgements

The EAS FHSC is an academic initiative that has received funding from a Pfizer Independent Grant for Learning & Change 2014 (No: 16157823) and from investigator-initiated research grants to the European Atherosclerosis Society/Imperial College London from Amgen, MSD, Sanofi-Aventis, Daichii-Sankyo and Regeneron. Prof KK Ray acknowledges support from the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre, United Kingdom. Ms KI Dharmayat acknowledges support from a PhD Studentship from the National Institute for Health Research (NIHR) under the Applied Health Research (ARC) programme for North West London, United Kingdom (the views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health). Prof T Freiberger was supported by a grant from the Czech Ministry of Health (No. NU20-02-00261). Prof J Genest receives support from the Canadian Institutes of Health Research. The Austrian FH registry has been supported by funds from the Austrian Heart Foundation and the Tyrolean Regional Government. The Gulf FH registry was conducted under the auspices of the Gulf Heart Association.

Data Sharing Statement

Data collected in the FHSC Registry cannot be shared with third parties owing to clauses in Data Sharing Agreements with Data Suppliers that do not allow this. Data ownership for the Data shared with the FHSC Registry remains the property of the Data Suppliers.

REFERENCES

1 Familial Hyperchcolesterolemia [FH]: Report of a WHO Consultation. World Health Organization, Human Genetics Programme, Division of Noncommunicable Diseases. WHO/HGN/FH/CONS/98.7. Geneva, 1998.

2 Representatives of the Global Familial Hypercholesterolemia Community, Wilemon KA, Patel J, Aguilar-Salinas C, et al. Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia: A Global Call to Action. *JAMA Cardiol* 2020; **5(2):** 217–29.

3 Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients with Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Circulation* 2020; **141(22):** 1742–59.

4 Nordestgaard BG, Chapman MJ, Humphries SE, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013; **34(45):** 3478-90a.

5 EAS Familial Hypercholesterolaemia Studies Collaboration, Vallejo-Vaz AJ, Akram A, Kondapally Seshasai SR, et al. Pooling and expanding registries of familial hypercholesterolaemia to assess gaps in care and improve disease management and outcomes: Rationale and design of the global EAS Familial Hypercholesterolaemia Studies Collaboration. *Atheroscler Suppl* 2016; **22:** 1–32.

6 Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol* 2012; **23(4):** 282–9.

7 Ruel I, Brisson D, Aljenedil S, et al. Simplified Canadian Definition for Familial Hypercholesterolemia. *Can J Cardiol* 2018; **34(9):** 1210–4.

8 Harada-Shiba M, Arai H, Ishigaki Y, et al; Working Group by Japan Atherosclerosis Society for Making Guidance of Familial Hypercholesterolemia. Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017. *J Atheroscler Thromb* 2018; **25(8):** 751–70.

9 Cuchel M, Bruckert E, Ginsberg HN, et al; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. 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(32):** 2146–57.

10 WHO regions. World Health Organization (WHO). [Last accessed Mar 18, 2021] https://www.who.int/about/who-we-are/regional-offices

11 Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *J Am Coll Cardiol* 2020; **75(20):** 2553–66.

12 EAS Familial Hypercholesterolaemia Studies Collaboration, Vallejo-Vaz AJ, De Marco M, Stevens CAT, et al; EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) Investigators. Overview of the current status of familial hypercholesterolaemia care in over 60 countries – The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Atherosclerosis* 2018; **277:** 234–55.

13 Watts GF, Gidding SS, Mata P, et al. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol* 2020; **17(6):** 360–77.

14 Besseling J, Huijgen R, Martin SS, Hutten BA, Kastelein JJP, Hovingh GK. Clinical phenotype in relation to the distance-to-index-patient in familial hypercholesterolemia. *Atherosclerosis* 2016; **246:** 1–6.

15 Pérez de Isla L, Alonso R, Mata N, et al; SAFEHEART Investigators. Coronary Heart Disease, Peripheral Arterial Disease, and Stroke in Familial Hypercholesterolaemia: Insights From the SAFEHEART Registry (Spanish Familial Hypercholesterolaemia Cohort Study). *Arterioscler Thromb Vasc Biol* 2016; **36(9):** 2004–10.

16 Beheshti S, Madsen CM, Varbo A, Benn M, Nordestgaard BG. Relationship of Familial Hypercholesterolemia and High Low-Density Lipoprotein Cholesterol to Ischemic Stroke: Copenhagen General Population Study. *Circulation* 2018; **138(6):** 578–89.

17 Hovland A, Mundal LJ, Igland J, et al. Risk of Ischemic Stroke and Total Cerebrovascular Disease in Familial Hypercholesterolemia. *Stroke* 2019; **50:** 172–4.

18 Mach F, Baigent C, Catapano AL, et al; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41(1):** 111–88.

19 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019; **139(25):** e1082–143.

20 Besseling J, Kastelein JJ, Defesche JC, Hutten BA, Hovingh GK. Association between familial hypercholesterolaemia and prevalence of type 2 diabetes mellitus. *JAMA* 2015; **313(10):** 1029–36.

21 Huijgen R, Kindt I, Fouchier SW, et al. Functionality of sequence variants in the genes coding for the low-density lipoprotein receptor and apolipoprotein B in individuals with inherited hypercholesterolaemia. *Hum Mutat* 2010; **31(6):** 752–60.

TABLES

Table 1. Characteristics of FH patients overall and stratified by geographical region.

Data shown as absolute and relative frequencies [n (%)] or median and interquartile range, as appropriate. (*) For Africa region, most cases (n=839, 99·4%) were from South Africa, the remaining corresponding to Nigeria. (a) Age at FH diagnosis and (b) body mass index data not available in most cases from the region of Africa. (c) Data not available in most datasets (primarily collected premature disease, instead of overall disease). (d) Information on peripheral artery disease was not available in the dataset from The Netherlands. Results for coronary artery disease, stroke and peripheral artery disease are excluding data from Egypt and Uzbekistan, since both datasets have "having premature cardiovascular disease" (any)as inclusion criteria. CAD, coronary artery disease; FH, familial hypercholesterolaemia; LLM, lipid-lowering medication.

Table 2. Characteristics of FH patients stratified by sex and by index case status.

Data shown as absolute and relative frequencies [n (%)] or median and interquartile range (IQR), as appropriate. FH: familial hypercholesterolaemia; LLM: lipid-lowering medication. Data with information available on index or non-index case n=26,735. FH: familial hypercholesterolaemia; LLM: lipid-lowering medication.

FIGURE LEGENDS

Figure 1. Distribution of participants by age and sex at entry in the registry (A) and at the time of FH diagnosis (B).

Inclusion criteria for the study was age at entry in the registry 18 years or older. FH, familial hypercholesterolaemia.

Figure 2. Cardiovascular risk factors (hypertension [A], diabetes [B] and body mass index overall [C] and by age [D]).

Categories of body mass index are defined as follows: "low weight", body mass index below 18·5 kg/m^2; "normal weight", 18·5 to <25 kg/m^2; "overweight", 25 to <30 kg/m^2; "obesity", 30 kg/m^2 or above. BMI, body mass index; IQR, interquartile range.

Figure 3. Cardiovascular disease by LDL-C levels among patients not on lipid-lowering medication.

p values are for the comparison across LDL-C categories within each cardiovascular disease group. (*) LDL-C cut-offs are based on the categories of LDL-C in the Dutch Lipid Clinic Network (DLCN) FH diagnostic criteria. LDL-C, low-density lipoprotein cholesterol.

Figure 4. Cardiovascular disease stratified by sex (panels A and B) and by index case status (panels C and D). A: Prevalence of type of cardiovascular disease stratified by sex; (B) Association of sex with type of cardiovascular disease; (C) Prevalence of cardiovascular disease among index and non-index cases; (D) association between of index/non-index cases with cardiovascular disease.

(*) Odds ratio adjusted by age, baseline comorbidities (hypertension, diabetes, smoking, body mass index), lipid levels (LDL-C, HDL-C, log[TG]), lipid-lowering medication, index case, and interaction between LDL-C and lipid-lowering medication. (**) Odds ratio adjusted by age, sex, baseline comorbidities (hypertension, diabetes, smoking, body mass index), lipid levels (LDL-C, HDL-C, log[TG]), lipid-lowering medication, and interaction between LDL-C and lipid-lowering medication. CAD, coronary artery disease; CI, confidence interval; IC, index case; OR, odds ratio.

Figure 5. Lipid-lowering medication: (A) Class and type of lipid-lowering medication; (B) Combination therapy among participants taking statins, ezetimibe or PCSK9 inhibitors.

LLM, lipid-lowering medication; PCSK9 inh, proprotein convertase subtilisin/kexin type 9 inhibitors; SD, standard deviation.

Figure 6. Attainment of LDL-C goals among patients on lipid-lowering medication: (A) Percentage of patients on lipid-lowering medication with an LDL-C below different thresholds; (B) Percentage of patients on lipid-lowering medication (statins, ezetimibe and/or PCSK9 inhibitors) with and LDL-C <1·8mmol/L based on the number of lipid-lowering medications taken; (C) Odds of attaining an LDL-C <1·8mmol/L based on the number of lipid-lowering medications taken (statins, ezetimibe and/or PCSK9 inhibitors; and (D) Odds of attaining an LDL-C <1·8mmol/L based on the type of lipid-lowering medication.

(*) Age and sex adjusted. (**) Each one adjusted by age, sex and the other types of lipid-lowering medication. Results for the LDL-C goal of <1·4mmol/L are shown in Supplemental Figure 7. CI, confidence interval; LLM, lipid-lowering medication; OR, odds ratio; PCSK9, proprotein convertase subtilisin/kexin type 9.