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Improving the global care of familial hypercholesterolaemia: Starting the ball rolling

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In 2013, a European Atherosclerosis Society (EAS) consensus panel concluded that familial hypercholesterolaemia (FH) was underdiagnosed and undertreated [1]. Supported by international evidence [2–5], the expert panel also recognised the worldwide shortfall of data on the care of FH.

1. The Familial Hypercholesterolaemia Studies Collaboration

To address this important demand, the Familial Hypercholesterolaemia Studies Collaboration (FHSC) was established under the auspices of the EAS in 2015. The primary aim of the FHSC is to improve global knowledge of the care of FH patients through the acquisition, curation and analysis of big data within a robust registry framework. The first publication hailed 'a call to arms' [6] to buttress critical gaps in the care of FH. The mission, aims and technical aspects of the FHSC registry have been published [7]. The registry harbours the largest global dataset on FH, derived from 70 countries across 6 continents.

This issue of *Atherosclerosis* includes a thematic series of 41 peer-assessed articles on diverse aspects of the care of FH, including the overview FHSC report and 5 invited reviews from leading experts in the field.

2. Overview report from the FHSC

The opening article from the FHSC presents the outcome of a survey relating to awareness, prevalence, management and treatment of FH across member countries. The report highlights a general lack of information on the prevalence of FH in most of the participating countries, and universally low rates of identification [8]. Where data are available, figures concur with contemporary estimates [9]. The distribution of plasma cholesterol in the community and specific characteristics, such as gene founder effects and consanguinity, and population sampling methods clearly influence the frequency estimates and detection rates of FH [8]. The survey shows that the Dutch Lipid Network Score is the most popular diagnostic tool, followed by Simon Broome and MEDPED; a minority of countries use modified criteria [2,10], highlighting the need for country-specific tools for FH diagnosis. Importantly, a critical observation is the lack of resources and funding to support best clinical practice in caring for FH. Genetic testing is not universally available and is used mostly to confirm clinical diagnosis; however, in the majority of cases, genetic testing is only self-funded or available in the context of research. About 30% of the countries surveyed offer genetic cascade screening mostly on a regional basis, with only a few at national level, but the funding formula is uncertain. Pharmacotherapies for manging FH are implemented in all countries, but are not universally reimbursed, re-imbursement criteria varying widely. High intensity statins are the standard of care, usually with add-on ezetimibe; in 4 countries, however, ezetimibe is not available. About 70% of the countries report availability of PCSK9-inhibitors, but use is restricted; 60% offer lipoprotein apheresis, but this is limited to one centralised or a few reference centres [8].

3. Epidemiology

The subsequent papers add to the evolving corpus of information referred to above. Several countries report that the community prevalence of FH is 2-fold greater than previously recognised [11–16]. This makes FH a public health issue that needs to be accordingly addressed. An expert review accepts the higher frequency of FH, but cautions that the data need to account for the method of diagnosis, ascertainment bias, gene founder effects, and consanguinity [17].

Several of the clinical surveys indicated that FH remains largely undiagnosed and untreated [12,18–27], despite meeting all the classical criteria for screening. The prevalence of definite FH is probably 5-fold higher among younger patients with an acute coronary syndrome [28] and protocols for linking the detection of such patients to follow-up in specialist clinics and the cascade testing of relatives for FH have been proposed [29]. The universal screening of children for FH has been championed in the UK and US [30], but only implemented and shown to be efficacious in Slovenia [31]. Universal screening of children, with reverse cascade testing of parents, has recently been shown to be cost-effective and deserves more consideration [32]. In WHO low-to-middle income countries, reverse cascade testing from a child with HoFH is an effective method of detecting high-risk family members [33]. Few reports give attention to the role of primary care in screening. This last topic is well reviewed by Brett et al. [34] who emphasized the value of opportunistic screening employing electronic data extraction

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tools, as exemplified by a report from Lithuania [35]. Multiple approaches to detecting FH have been proposed; selective, opportunistic, systematic and universal strategies all have merits and are not mutually exclusive [1,2,34,36].

4. Diagnostic tools

Whilst the Dutch Lipid Clinic Network criteria are most popular for diagnosing FH [8], but lack of information assails making an accurate diagnosis of FH [37]. Concordance with the Simon Broome and MEDPED criteria can also be moderate to low [38]. The Canadian network has therefore developed a simple and robust algorithm for diagnosing FH [39]. Whether this could provide a new standard diagnosis for FH remains to be verified. Country-specific criteria for FH are essential, particularly since there can be wide geographical variation (e.g. Europe and US vs Asia) in the population percentile values for LDL-cholesterol concentrations [8,10]. A practical definition of homozygous FH is also required [4], noting the phenotypic diversity of condition [40].

5. Genetic testing

Best practice in precision medicine requires that the diagnosis of FH be confirmed genetically [41]. Several countries have therefore undertaken their own genetic studies, supported in some cases by international experts [11,16,31,33,37,42–45]. Genetic testing is important in countries with high rates of consanguinity [42]. Next generation sequencing permits the detection of a wider spectrum of mutations [11,16,44,45] that not only facilitate a definitive diagnosis of FH, but may also confirm polygenic hypercholestrerolaemia; this molecular diagnosis may predict a more adverse prognosis in FH or when isolated may be used to ration cascade testing [46]. Genetic testing is acceptable and does not impair quality of life, which is more likely consequent on co-existent morbidities in FH [47].

6. Risk stratification

The clinical expression of FH is variable and cardiovascular (CV) risk equations have been described [48]. Several reports show a high prevalence of non-cholesterol risk factors among patients with FH, implying the need to address targets beyond LDL-cholesterol [18,20,23–26,49]. Smoking remains a major driver of CV risk across all continents [25,49], providing a major mandate for coronary prevention in FH. Diabetes and hypertension are also major priorities and the prevention of obesity a critical lifestyle objective in children with FH. The roles of Lp(a) [50], cardiac imaging [51] and genetic testing [41] in risk prediction are increasingly being recognised, but were not specifically covered in this first cluster of country reports. Lp(a) evidently needs to be accounted for when making the phenotypic diagnosis of FH [52] and its complex with PCSK9 in plasma [53] could partly explain the reduction in Lp(a) with PCSK9 mAbs against background statin therapy [54].

7. Treatment targets, gaps and guidelines

Therapeutic targets and novel therapies for FH are well reviewed by Raal et al. [55]. Reaching LDL-targets remains a universal challenge in managing FH [18,20,23–26,49] and requires not only overcoming cost and access barriers to PCSK9 inhibitors, but also addressing the beliefs and perceptions of patients concerning medication [56]. Treatment gaps and related gender and ethnic disparities in the use of statins and attainment of treatment targets have also been underscored by data from the CASCADE-FH Registry in the US [57,58]. The ideal LDL-targets for FH patients may require revision in light of new clinical outcome trials with PCSK9 inhibitors. Current lipid management guidelines will need updating in 2019 [55,59].

Dedicated clinical services for FH can evidently achieve better treatment outcomes in FH [22,25–27,31]. In low-to-middle income countries there is a major need to improve the care for severe FH [33] and international advocacy for government funding for apheresis and new therapies is paramount. However, even in countries where apheresis is funded [25], homozygous FH patients remain non-receptive to this form of therapy. This emphasizes the importance of improving physician training and expertise and addressing patient perceptions and beliefs about treatment [56]. The optimal management of FH in pregnancy needs further delineation, but preliminary data from a selected series in South Africa suggests that statins may be used safely from the third or fourth month of pregnancy [60]. Lipoprotein apheresis, however, remains a cornerstone of management of women with FH and coronary artery disease during pregnancy [61].

8. Role of community care

Models of care for FH should ideally be integrated across medical disciplines [2]. International guidelines recommend that most patients should be managed in primary care [1–3], noting that FH is a public health issue that accordingly needs addressing through several approaches to screening in the community [34]. While general practitioners, or family doctors, are ideally suited to detecting cases and caring for families with FH, their knowledge and practice remain suboptimal, but this can be partly remedied through dedicated vocational training and accreditation in FH [62]. Brett et al. [34] outline a comprehensive research agenda for primary care that encompasses several epidemiological, clinical (diagnostics, risk prediction, intervention trials), patient-centric and service design aspects of FH. This template can be adapted to set more general research priorities for the FHSC network.

9. Patient support groups and networks

Patient support groups and networks are essential for advocating critical improvements across the continuum of care of FH [2,30]. Their value is well reviewed by an international consortium representing countries across Europe and North America [30]. The many achievements of these patient networks to date encompass government support for screening programmes, development of risk prediction tools, improvements in access to new therapies, support for patient registries, and recognition of a new ICD-10 code for FH.

10. Registries

Registries are important not only to raise awareness of FH, but also to garner information necessary for clinical trials and audits, for education of registrants and healthcare professionals, and for health service research and policy making [8,63]. FH registries reported in this series are at different stages of development [16,18,20,21,24–27,31,37,39,64]. Through the FHSC there are abundant opportunities for enabling the development of fledgling registries. This could take the form of providing support and advice on registry governance, standardization of data elements, interoperability and expansion of platforms, with the ultimate aim of curating and analysing the highest quality big data required for maximising impact on the care of FH. Integration with other large international registries remains a future objective [48,57,65].

11. Information gaps, more research and future reports

While a laudable initial set of papers are presented from the constituent member countries of the FHSC [8], selected gaps in information and desirable data for future communications should be identified. More registry data are required on the care of children with FH [36], such an initiative being currently spearheaded by Humphries, Wiegman and colleagues [66,67]. The population frequencies of FH need to be