FINAL REPORT

Translational Research for Improving the Care of Familial Hypercholesterolaemia: The "Ten Countries Study"

Investigators

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Abstract

Purpose: Familial hypercholesterolemia (FH) is the most common and serious form of inherited hyperlipidaemia. Dominantly inherited with high penetrance, untreated FH leads to premature death from coronary artery disease due to accelerated atherosclerosis from birth. Despite its importance, there is still a major shortfall in awareness, detection and treatment of FH worldwide. International models of care for FH have recently been published, but their effective implementation requires the garnering of more knowledge about the condition.

Scope: The "Ten Countries Study" aimed to investigate diagnostic, epidemiological and service aspects, as well as physician practices and patient experiences of FH in several countries in the Asia-Pacific Region and the Southern Hemisphere.

Methods: Five observational studies were undertaken (June 2014 – July 2016) to systematically investigate the following aspects of FH: the phenotypic predictors of low-density lipoprotein receptor mutations, the point prevalence in available community populations, current knowledge and clinical practices among primary care physicians, availability and utilisation of services and facilities, and patient perceptions and personal experiences of the condition.

Results: The studies identified the plasma LDL-cholesterol that best predicts a mutation, the community point prevalence of FH, that there are substantial deficits in the awareness and knowledge of FH among physicians, that there are important gaps in services and facilities for FH management and that patient attitudes and beliefs toward treatment and behaviours are the key determinants of intentions to engage in treatment and self-management behaviours in FH.

Conclusions: The results from these potentially inform better clinical practice and will enable the development of country-specific models of care for FH.

Key Words: familial hypercholesterolaemia, Asia-Pacific, translational research

Purpose

Objectives of Study:

Study Number	Title	Aim	Translational Value
1	Plasma LDL-cholesterol as a predictor of FH mutations	To select a level of plasma LDL-cholesterol that has the highest sensitivity and specificity in predicting a mutation in different countries.	The data inform a simple screening test for FH, based on LDL-cholesterol measurement, for use in primary care and where genetic testing is not available.
2	Prevalence of FH in community populations	To assess the prevalence of FH in adult and childhood populations.	The data emphasize the public health problem presented FH, including the shortfalls in detection and treatment. This will inform screening programs for FH in the community.
3	Knowledge and practices of Primary Care Physicians (PCPs) concerning FH	To determine awareness, knowledge and practices regarding FH in PCPs; and conduct a comparison across the centres in the region.	Defining the role of PCPs in the care of FH is essential for developing multi-disciplinary and integrated total quality management. Assessing current knowledge and practices is the starting point. The information can be employed to design effective teaching and training modules for PCPs in the detection and management of FH.
4	Comparison of services and facilities for the care of FH	To describe and compare existing health services, facilities and resources for the care in FH in the region.	The study provides international benchmarking of performance in health care for FH. It identifies and promotes successful strategies within a context that takes into account cultural, economic and logistic differences and create opportunities for implementing country-specific or region-specific models of care for FH.
5	Patient perceptions and personal experiences of FH	To investigate the association between patients' psychological factors and key behavioural and clinical outcome variables salient to the management of FH; and conduct a comparison across the centres in the region.	The study identifies the key psychological factors associated with compliance and patient decisions. The factors can then be used as a basis for behavioural interventions to promote better treatment compliance and patient decisions. Findings may also identify key populations within FH patients that should be prioritised e.g. those with low health literacy.

Study 1 Screening and diagnostic testing: LDL-cholesterol as a predictor of FH mutations

Scope

Familial hypercholesterolaemia (FH) specifically elevates plasma LDL-cholesterol concentration owing to the decreased uptake of LDL, mediated by the ligand apoB-100 for the LDL receptor. Diagnostic accuracy relies on identifying a causative mutation [1-3]. Most mutations causing FH occur in the *LDLR* (encoding low-density lipoprotein receptor) and fewer in *APOB* (encoding apolipoprotein B) and *PCSK9* (encoding proprotein convertase subtilisin/kexin type 9) [1, 4, 5]. The prognostic importance of identifying a genetic mutation causative of FH in patients with profound hypercholesterolaemia in the community has recently been underscored [6]. However, genetic testing is often prohibitively expensive and not commonly available, particularly in primary care and in Asian centres. The diagnostic thresholds of untreated LDL-cholesterol have not been defined in relation to their ability to predict a pathogenic FH mutation. Phenotypic criteria also require detailed family history and detection of occasionally subtle physical signs, such as arcus cornealis or xanthomata; these may not be easily detectable and their age-dependence invalidates them as criteria for the early detection of FH [2, 3, 7]. A recent study from South Korea demonstrated that traditional criteria have limited detection power and low specificity for mutations in their population [8]. This underscores the need for region- or country-specific criteria and guidelines. We aim to inform a first-step screening test for FH, based on LDL-cholesterol measurement, for use in primary care.

Methods

This study involved countries where genetic testing is available for clinical or research purposes (Australia, Hong Kong, Brazil and New Zealand). The cross-sectional investigation aims to select a level of plasma LDL-cholesterol that has the highest sensitivity and specificity in predicting a pathogenic mutation. Adults who have provided informed consent for genetic testing and collection of phenotypic data were studied. LDL-cholesterol levels from a fasting blood sample at screening was adjusted if required for type and dose of cholesterol-lowering drugs [9]. Mutational analyses for defects in the *LDLR, APOB* and *PCSK9* genes and assessment of pathogenicity have been uniformly carried out as described elsewhere [5, 10-12].

The ability of plasma LDL-cholesterol concentration to predict a genetic variant will be investigated using receiver operator characteristic (ROC) curves. The best value of LDL-cholesterol for predicting a mutation will be defined as a having highest sum of sensitivity and specificity. The effect of other variables (such as family and personal history of high cholesterol or coronary heart disease, physical signs and ethnicity) on the sensitivity and specificity of the LDL-cholesterol threshold will also be tested by multiple logistic regression analysis.

Results

The preliminary analyses from Australia and Brazil demonstrated an ROC of 0.8157 and 0.7053 with an LDL-cholesterol of 7.1mmol/L and 7.8mmol/L, respectively, in index cases and an ROC of 0.9371 and 0.8396 with an LDL-cholesterol of 4.8mmol/L and 4.9mmol/L, respectively, in relatives as predictors of FH mutations. We plan to further investigate the effect of other variables and compare across the participating countries.

Study 2 Epidemiology: Prevalence of FH in community and high risk populations

Scope

Excluding rare populations subject to a gene founder effect in whom FH is particularly common, the community prevalence of FH is estimated to be 1 in 500, with reports varying from 1 in 200 to 1 in 2000 [13]. Prevalence data enable the design of screening programs for FH in the community [14].

Methods

The point prevalence was calculated as the number of persons with FH divided by number of persons in the population, in several community cohorts from Australia and China.

FH was defined phenotypically, using a modified Dutch Lipid Clinic Network (DLCN) definition: premature family history of coronary artery disease (at age <55 years for men, <60 years for women) or premature death in a parent (father <55 years, mother <60 years) (1 point); personal history of coronary artery disease (2 points), personal history of stroke (1 point); plasma LDL-cholesterol >8.5 mmol/l (8 points), 6.5-8.4 (5 points), 5-6.4 mmol/l (3 points), and 4-4.9 mmol/l (1 point). Individuals on cholesterol-lowering therapy (almost exclusively statins) had their plasma LDL-cholesterol conservatively adjusted by a factor of 1.43 to estimate pre-treatment. FH was defined as: definite, score >8; probable, score 6-8; possible, score 3-5; and unlikely, score <3. In this study, phenotypic FH was defined as a score >5. Point prevalence of FH was age-standardised. In children, FH was defined as a LDL-cholesterol >4.0 mmol/L on 2 occasions with a family history of premature CHD (men <55 years, women <60 years old) and/or high cholesterol in at least 1 parent.

In the Chinese cohort, an LDL-based definition as well as a modified definition of the DLCN based on the 95th centile of LDL-cholesterol among the Chinese [LDL-cholesterol >6.0 mmol/L (8 points), 5.0–5.9 mmol/L (5 points), 3.5–4.9 mmol/L (3 points), or 2.5–3.4 mmol/L (1 point)]. The following LDL based definition of FH was employed: LDL-cholesterol≥ 6 mmol/L or LDL-cholesterol≥ 3.5mmol/L plus a personal or family history of premature coronary heart disease. Age standardisation was applied using the 2000 Chinese census data.

Results

In China and Australia, the prevalence of heterozygous FH was found to be 1:211-359 [15] and 1:229-353 [16], respectively, consistent with recent findings from the US [17] and Europe [18, 19]. In children in Australia we also found a frequency of FH of 1 in 267 [20]. The apparent higher frequency of FH in community populations have also been well evidenced by two recent studies employing genetic testing [6, 18]. Data from all countries appear to consistently indicate under-diagnosis and under-treatment of FH across all ages and ethnic groups. The prevalence of FH in coronary care units is also informative for targeted screening for index cases. In Australia [21], 14.3% of coronary patients aged less than 60 years were found to have phenotypic FH. These data concur with reports from Europe [22]. Coronary care screening for FH in the region is also warranted.

There was a lack of good epidemiological data in other countries to assess FH prevalence.

Study 3 Education and training: Knowledge and practices of FH among physicians

Scope

The majority of people in the community will have contact with their primary care physician (PCP) or family doctor. PCPs can perform absolute cardiovascular risk assessments and are well placed to opportunistically detect FH [23, 24]. Well controlled and low complexity patients, initially identified in specialist centres, should be transitioned if feasible to primary care for long-term management or for shared care, while high complexity patients should be followed-up by the specialist service [2]. The role of primary care in the care of FH has not been adequately defined. A preliminary study suggested a significant shortfall in awareness, knowledge and practices among family doctors in the Asia-Pacific region [25, 26]. Defining the role of PCPs in the care of FH is essential for developing multidiscplinary and integrated total quality management. Assessing current knowledge and practices is the starting point.

Methods

A formal questionnaire was offered to PCPs via cardiovascular education sessions and/or mail lists from the royal colleges (or country equivalent). Completion of the survey is voluntary and anonymous. The survey enquired about the following elements: general familiarity with FH; awareness of national and international guidelines for FH;, the clinical description of FH; identification of the typical lipid profile; prevalence and inheritance of FH; extent of elevation in risk of CVD, definition of premature CVD and physical features in FH; whether the diagnosis requires genetic confirmation; methods for alerting PCPs about the possibility of FH; type of health professional best placed to detect FH; number of patients with FH currently being treated; specific treatments; knowledge and practices concerning family screening; treatment and referral practices regarding patients with severely elevated cholesterol. Also recorded are demographic data including gender, qualifications and training status, years of experience, and size and location of practice.

Results

1,497 physicians completed the questionnaire with only 34% considered themselves to be familiar with FH. 75% correctly defined FH and 63% identified the typical lipid profile, with a higher proportion of physicians from United Kingdom, China and Japan selected the correct FH definition and lipid profile compared with those from South Korea, India and Vietnam. However, less than half of the physician across the 10 countries were aware of national or international management guidelines (39%), or correctly defined the prevalence (27%), inheritance (41%), and CVD risk of FH (10%). 57% suggested PCPs as the most effective health professional to detect FH. The majority of the physicians also considered laboratory interpretative comments are useful (82%) and statin therapy is an appropriate cholesterol-lowering therapy (91%) for FH management.

The study identified substantial deficits in the awareness and knowledge of FH among physicians in the region. Implementation of country-specific guidelines and extensive work in FH education and awareness programs are essential to improve the care of FH.

Study 4 Health service research: Comparison of services and facilities for the care of FH

Scope

In spite of the increasing recognition of the importance of FH, the care of patients and families remains suboptimal [2, 3]. Services need improvement and standardisation at several levels [10, 27]. This includes paediatric services, cascade screening and multidisciplinary care that involves laboratory medicine, cardiology and transfusion medicine. Close collaboration between healthcare systems, patient support groups and non-government organizations is essential [2]. A clinical registry can also provide invaluable information for research and audit, as well as for improving the quality of care. There are no published data describing or comparing healthcare resources for the detection and management of FH across different countries with diverse healthcare systems. This project will provide knowledge that could form an international benchmark for future performance in the care of FH. The knowledge will be generated within a context that takes account of cultural, economic and logistic differences and will create opportunities for implementing country-specific or region-specific models of care for FH. It will promote regional and international collaboration that could greatly enhance the development of new services for FH where gaps are identified.

Methods

The project was based on an on-line questionnaire that specifically investigates the key dimensions of a desirable model of care [2, 28, 29] . The survey was completed voluntarily by the main key opinion leaders (KOLs), or experts, in FH in the region; a minimum of 3 KOLs per country. The enquiry related to the following elements: national guidelines and protocols, medical specialties involved in care, role of primary care, screening, diagnostic and assessment protocols, DNA testing facilities, paediatric services, therapeutic strategies, apheresis and liver transplantation; clinic support (nurses, dieticians, counsellors, information technology and registry), biochemistry laboratory services, cardiology services, funding (public, private, health insurance), drug re-imbursement, education and training programmes, research programmes, links with and support from government and non-government organisations, and existence of a family support group [2, 27, 29].

Results

94 leading experts in FH completed the questionnaires. Of the 15 countries or regions studied, 45% had established national guidelines and protocols for FH management. Only 30% had a network of lipid clinics. More than half of the countries provided genetic (53%) and paediatric services (66%) to FH patients. Formal LDL apheresis service was only available in 7 countries (45%). All 15 countries or regions had cardiovascular imaging facilities available for FH patients. Australia, United Kingdom and Japan are the three countries providing all six services and facilities to FH patients. In contrast, the care of FH in Vietnam and the Philippines is suboptimal with less than three services and facilities available in their countries.

This survey has identified important gaps in services and facilities for FH management. Further focus on implementation of national management guidelines, lipid clinic network and apheresis facilities are required, particularly in less developed countries.

Study 5 Health psychology: patient perceptions and personal experiences of FH

Scope

Numerous psychological factors have been found to be associated with salient adaptive outcomes and individual patient-related behaviours linked with successful treatment and management of FH [30]. Current research suggests that attitudes and beliefs about the severity of FH predict intentions and motivation to engage in treatment, particularly adherence to lipid-lowering drug regimens and self-management behaviours like physical activity and diet [31]. However, much of the research has been conducted in relatively small samples using qualitative methods [32]. Other additional psychological factors that may be related to important outcomes related to the management of illness should be investigated in FH patients. These include facilitating factors and barriers to compliance with behavioural therapy and lifestyle change, particularly among those who do not have any clinical manifestation of the illness and are asymptomatic, [33] and knowledge of the illness, medication, and health literacy. In addition, factors that may affect adherence to treatment, including beliefs about the controllability of the illness and efficacy of medication, should be identified and investigated. The project identifies key psychological factors associated with adherence and patient decisions to consent to refer relatives for cascade testing for FH. The factors can then be used as a basis for behavioural interventions to promote better care of families with FH.

Methods

Participants were recruited from regional clinics managing FH patients in different countries. Volunteer patients with FH will be recruited via clinic staff who will offer them the opportunity to participate. The study adopted a correlational, quantitative design in which psychometric measures of key psychological and behavioural variables were elicited from samples of FH patients. The factors include attitudes, motives and beliefs toward treatment including drug and self-management behaviours, beliefs in medication, FH illness perceptions and beliefs about treatment and medication, health literacy and intentions to participate in physical activity, eat a healthy diet, and take FH medication. Measures were be based on previous research and informed by a preliminary qualitative study [34]. Key clinical and behavioural outcomes were collected from patient records in the collaborating clinics. Language-specific versions of the questionnaire was developed from the English-language version using standardized back-translation techniques with the aid of bilingual translators.

Results

The pilot study in Australia [35] demonstrated that patient attitudes and beliefs toward treatment and behaviours rather than beliefs about the illness are the key determinants of intentions to engage in treatment and self-management behaviours, suggesting that changing attitudes and beliefs toward the behaviours may be a priority for promoting better management of FH.

Comparisons of the key psychological correlates of treatment and management behaviours and outcomes across the different countries is of particular interest as it will facilitate understanding of the cultural influences on living with, treating, and managing FH. We plan

to investigate and compare the effects of the effects of the psychological factors on behaviours and outcomes among the participating countries. We anticipate three potential contributions:

(1) Effects of patient beliefs about FH management behaviours and beliefs about FH on intentions to participate in behaviours. We aim to replicate the initial study on the Australian data across participating countries from the study. Specifically we will compare effects of two sets of perceptions: beliefs about self-management behaviours (medication adherence, physical activity participation, eating healthily) and beliefs about FH on self-reported behaviour across the national groups. In practice, this means replicating the analyses of the pilot study in Australia and comparing the strength of the effects across national groups. This will provide important information on the extent to which cultural differences affect the psychological factors that determine FH management.

(2) Effects of health literacy and illness beliefs on quality of life and general health in FH patients. This will establish the extent to which health literacy determines adaptive outcomes in FH patients which have implications for effective clinical management. Critically, we want to provide formative evidence as to whether promoting adaptive beliefs about FH can mediate the effects of health literacy on the outcomes.

(3) Effects of treatment beliefs and illness beliefs on self-management behaviours. Concerns over use of medication (e.g., worries about side effects) and necessity (e.g., beliefs about effectiveness) may affect medication adherence. We will examine the effects of these factors on intentions to take medication in samples from all national groups. Findings are expected to inform in-clinic practice on how best to frame medications to patients so that they will be more likely to adhere to their regimen over time.

Overall Conclusion:

The “Ten Countries Study” is the first collaborative effort relating to FH of countries in Asia and the Southern Hemisphere. The series of five studies have garner new knowledge that is likely to enhance the care of patients and families with FH in a region that has the highest density of people with the condition. It is also likely to inform better clinical practice and the development of country-specific models of care for FH.

The full collation of data and analyses will be completed in the second half of 2016; some findings have already been published (see List of Publications).

List of Publications:

- Shi Z, Yuan B, Zhao D, Taylor AW, Lin J and Watts GF: Familial hypercholesterolemia in China: Prevalence and evidence of underdetection and undertreatment in a community population. Int J Cardiol, 2014; 174:834-836
- Pang J, Sullivan DR, Harada-Shiba M, Ding PY, Selvey S, Ali S and Watts GF: Significant gaps in awareness of familial hypercholesterolemia among physicians in selected Asia-Pacific countries: A pilot study. J Clin Lipidol, 2015; 9:42-48
- Watts GF, Shaw JE, Pang J, Magliano DJ, Jennings GLR and Carrington MJ: Prevalence and treatment of familial hypercholesterolemia in Australian communities. Int J Cardiol, 2015; 185:69-71
- Pang J, Martin AC, Mori TA, Beilin LJ and Watts GF: Prevalence of familial hypercholesterolaemia in adolescents: potential value of universal screening? The Journal of Pediatrics, 2016; 170:315-316
- Hagger MS, Hardcastle SJ, Hingley C, Strickland E, Pang J and Watts GF: Predicting Self-Management Behaviors in Familial Hypercholesterolemia Using an Integrated Theoretical Model: the Impact of Beliefs About Illnesses and Beliefs About Behaviors. International Journal of Behavioral Medicine, 2016; 23:282-294
- Hu M, Hooper AJ, Bockxmeer FM, Watts GF, Chan JC and Tomlinson B: Management of Familial Hypercholesterolemia in Hong Kong. J Atheroscler Thromb, 2016; 23:520-531
- Pang J, Lansberg PJ and Watts GF: International Developments in the Care of Familial Hypercholesterolemia: Where Now and Where to Next? J Atheroscler Thromb, 2016; 23:505-519
- Rangarajan N, Balasubramanian S, Pang J and Watts GF: Knowledge and Awareness of Familial Hypercholesterolaemia among Registered Medical Practitioners in Tamil Nadu: Are They Suboptimal? Journal of Clinical and Diagnostic Research, 2016; 10:OC52-56
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- Watts GF, Ding PYA, George P, Hagger MS, Hu M, Lin J, Khoo KL, Marais AD, Miida T, Nawawi HM, Pang J, Park JE, Gonzalez-Santos LB, Su TC, Troung TH, Santos RD, Soran H, Yamashita S, Tomlinson, B: Translational Research for Improving the Care of Familial Hypercholesterolaemia: The "Ten Countries Study" and Beyond'. J Atheroscler Thromb, 2016; 23: *accepted manuscript*

Additional Outcomes:

- New countries were recruited to the project: Vietnam, the UK, India and Singapore
- Investigator meetings were held at the:
    - 17th International Symposium on Atherosclerosis (ISA), Amsterdam, May 2015
    - 47th Annual Scientific Meeting of the Japan Atherosclerosis Society (JAS), Sendai, July 2015
    - 84th European Atherosclerosis Society (EAS) Congress, Innsbruck, May-June 2016
    - 10th Congress of the Asia-Pacific Society of Atherosclerosis and Vascular Diseases (APSAVD), Tokyo, July 2016
- Three abstracts were presented at the 84th EAS Congress, Innsbruck, May-June 2016
    - Abstract 1: International Comparison of Primary Care Knowledge and Practices of Familial Hypercholesterolaemia – presented by Dr Jing Pang
    - Abstract 2: International Comparison of Services and Facilities for the Care of Familial Hypercholesterolaemia – presented by Dr Jing Pang
    - Abstract 3: Predicting Familial Hypercholesterolemia Patients' Quality of Life and Self-Assessed Health: Illness Beliefs, Beliefs about Medication, and Health Literacy – presented by Prof Martin Hagger
- A "10 Countries Study" workshop and two abstracts were presented at Anitschkow Days – Symposium of the International Atherosclerosis Society, St Petersburg, June 2016
- The "10 Countries Study" group was invited to join the FH Studies Collaboration (FHSC) of the EAS
- Book: Parhofer K and Watts G: Essentials of Familial Hypercholesterolemia, Springer Healthcare Ltd, 2014
    - Electronically at the 2nd World Congress of Clinical Lipidology, Vienna, December 2014
    - Physically distributed at the JAS meeting in Sendai, July 2015
- Special initiatives: a "10 Countries Exchange Program" was setup, in conjunction with APSAVD, to assist researchers to embark on a short-term exchange program to extend and enhance knowledge, research and collaboration between centres within the "10 Countries Study".
- Publication plans: four publications in the pipeline for Study 1, 3, 4 and 5, expected completion December 2016.
- Parallel developments: an Asia-Pacific web-based Registry is in the planning phase.

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