American Heart Journal Plus: Cardiology Research and Practice 13 (2022) 100097

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

The design and rationale of the Advancing Cardiac Care Unit-based Rapid Assessment and Treatment of hypErcholesterolemia (ACCURATE) study

Junran J. Peng [a,1], Navid Saleh [a,1], Thomas M. Roston [a], Adam Kramer [a], Lubomira Cermakova [b], G.B. John Mancini [a,c], Christopher B. Fordyce [a,c,d], Liam R. Brunham [a,e,f,*]

[a] Department of Medicine, University of British Columbia, Vancouver, BC, Canada
[b] Healthy Heart Program Prevention Clinic, St. Paul's Hospital, Vancouver, Canada
[c] Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada
[d] Centre for Health Evaluation & Outcomes Sciences, University of British Columbia, Vancouver, BC, Canada
[e] Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada
[f] Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada

ARTICLE INFO

Keywords:
Acute coronary syndrome
Lipids
Lipoproteins
Genetics
Familial hypercholesterolemia
Coronary artery disease

ABSTRACT

Familial hypercholesterolemia (FH) is an inherited condition characterized by elevated low-density lipoprotein cholesterol (LDL-C) levels and premature atherosclerotic cardiovascular disease (ASCVD). Despite being the most common inherited cardiovascular disorder, it is still highly underdiagnosed and undertreated worldwide. We designed the Advancing Cardiac Care Unit-based Rapid Assessment and Treatment of hypErcholesterolemia (ACCURATE) study to test the hypothesis that opportunistic genetic testing for FH among patients hospitalized for acute coronary syndrome (ACS) will increase the diagnosis of FH and improve patient outcomes. ACCURATE is a non-randomized, controlled trial of patients <60 years old admitted to an acute cardiac unit with ACS and elevated LDL-C levels. The first cohort will consist of a control group of patients presenting with ACS who will be treated according to usual standard-of-care. The second cohort will consist of patients presenting with ACS in whom research-based genetic testing for FH will be performed during hospitalization and the results returned to the treating physicians. The primary endpoint will be the number of patients with a new diagnosis of FH. The secondary endpoints will be the proportion of patients who undergo intensification of lipid-lowering therapy, the lowest LDL-C level achieved, and the proportion of patients reaching guideline recommended lipid targets in the 12 months after the index ACS. To our knowledge, ACCURATE represents the first clinical trial of genetic testing for FH in the acute cardiac care setting and is expected to help identify optimal approaches to increase the diagnosis and treatment of FH.

1. Introduction

Familial hypercholesterolemia (FH) is the most common inherited cardiovascular disorder and is characterized by a lifelong increase in low-density lipoprotein cholesterol (LDL-C) and increased risk of atherosclerotic cardiovascular disease (ASCVD). Worldwide, FH affects 1 in 313 individuals in the general population, and 1 in 15 individuals with premature ischemic heart disease [1]. However, FH is significantly under-detected, with an estimated 99% of patients worldwide remaining undiagnosed [2]. This underdiagnosis limits the ability to optimally treat patients as well as to perform cascade screening, which can identify other affected relatives for whom primary preventative therapies can significantly reduce the risk of ASCVD [3].

One strategy to increase the identification of patients with FH is opportunistic screening of patients presenting with an acute coronary syndrome (ACS). This strategy is premised on the observation that FH is common among patients with ACS, and particularly in those of younger age. A systematic review and meta-analysis reported that 1 in 14 patients presenting with an ACS under 60 years of age has FH, and this increases to 1 in 7 in those under 45 years of age [4]. These observations suggest that the yield of systematic testing in this population would be high. However, there is a paucity of prospective data to support this

* Corresponding author at: Centre for Heart Lung Innovation, Room 166-1081 Burrard Street, Vancouver, BC V6Z 1Y6, Canada.
E-mail address: liam.brunham@ubc.ca (L.R. Brunham).
[1] Joint first authors.

https://doi.org/10.1016/j.ahjo.2022.100097
Received 19 November 2021; Received in revised form 12 January 2022; Accepted 18 January 2022
Available online 4 February 2022

strategy. Focusing on patients with a recent ACS is also relevant because of the very high cardiovascular risk of this population, relative to patients with more stable forms of ASCVD [5].

FH is diagnosed based on a combination of clinical, biochemical, and, when available, genetic features. The most commonly used diagnostic criteria are the Dutch Lipid Clinic Network Criteria (DLCN), the Simon Broome Register group, the Make Early Diagnosis Prevent Early Death (MEDPED) criteria, the Canadian Definition of FH, and others [6]. In most of these criteria, the finding of a pathogenic DNA variant in the *LDLR*, *APOB* or *PCSK9* genes establishes a diagnosis of 'definite' FH [6–8]. Clinical practice guidelines recommend the use of genetic testing to facilitate the diagnosis of FH [9]. Genetic testing for FH also enables cascade testing of asymptomatic family members who may be eligible for primary preventative therapies [10]. Despite these advantages, genetic testing for FH is unavailable in many jurisdictions and is underused in the diagnosis of FH [11].

Here we report the design and rationale of the Advancing Cardiac Care Unit-based Rapid Assessment and Treatment of hypErcholesterolemia (ACCURATE) study. We designed ACCURATE as a controlled, non-randomized trial to assess the hypothesis that genetic testing among patients hospitalized for an ACS will improve the diagnosis of FH and enhance therapeutic decision-making and treatment outcomes.

2. Methods

ACCURATE has been approved by the Providence Health Care Research Ethics Board (certificate # H21-00116-A001), and all patients will provide written, informed consent prior to enrollment. The trial will be conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonization "Good Clinical Practices".

2.1. Study overview and objectives

The ACCURATE study is a multi-site, prospective, non-randomized clinical trial assessing the use of research-based genetic testing of FH in patients admitted to an acute cardiac unit at Vancouver General Hospital (VGH) or St. Paul's Hospital (SPH) in Vancouver, Canada. An overview of the study flow is presented in Fig. 1. Two sequential groups of patients will be studied. Cohort 1 (Control group) will consist of patients meeting the inclusion criteria (Table 1) who will be recruited over the first 6 months of the study and treated according to local standard-

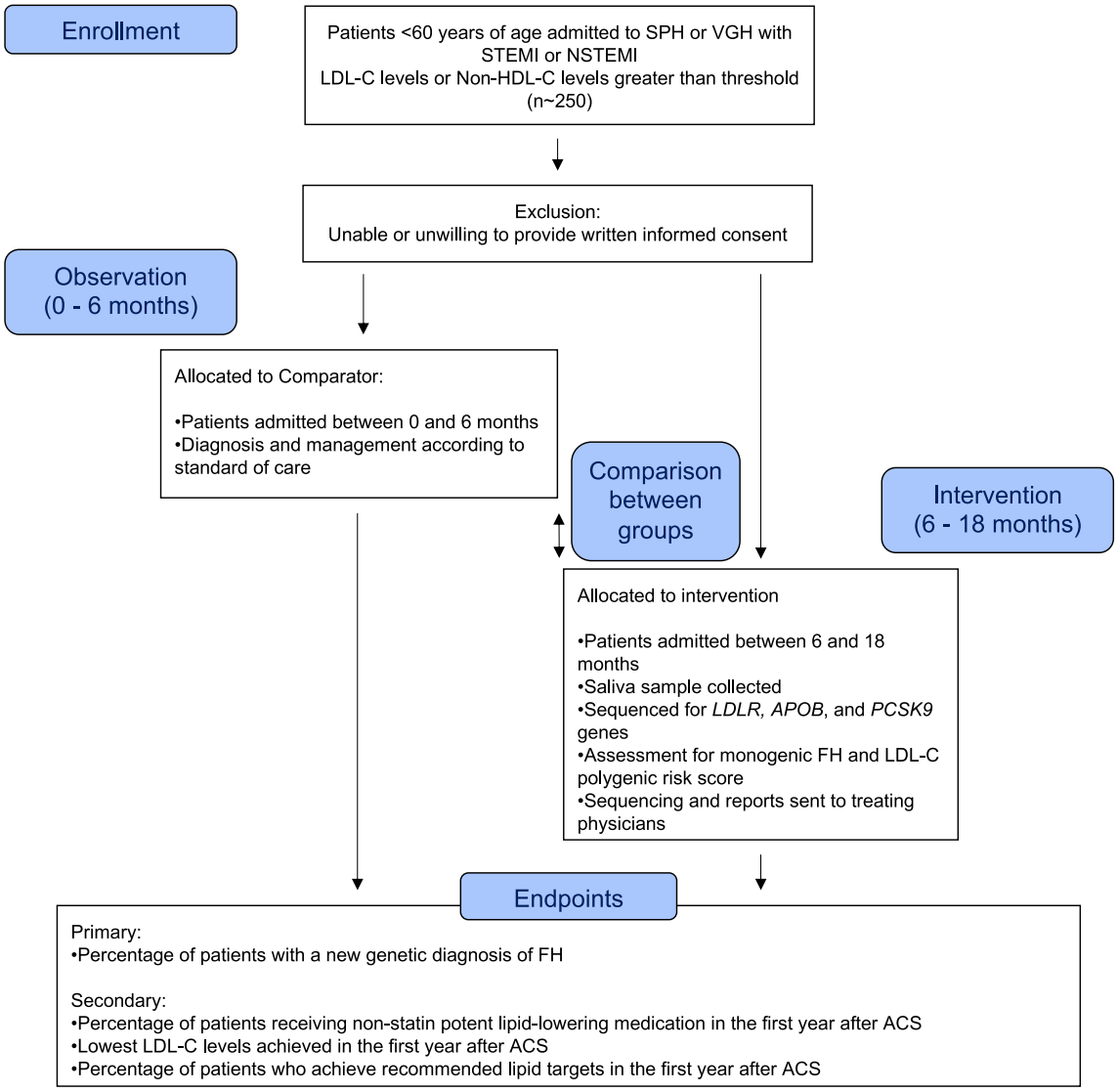

Fig. 1. Overview of study workflow. Abbreviations: STEMI, ST-elevated myocardial infarction; NSTEMI, non-ST-elevated myocardial infarction; LDL-C, low-density lipoprotein C; EMR, electronic medical record; LDLR, low-density lipoprotein receptor; APOB, apolipoprotein B; PCSK9, proprotein convertase subtilisin/kexin type 9; FH, familial hypercholesterolemia; ACS, acute coronary syndrome.

Table 1
Inclusion and exclusion criteria for patient recruitment in the ACCURATE study.

Inclusion criteria	Exclusion criteria
Age < 60 years	Unable or unwilling to provide written, informed consent
Lipid levels • LDL level ≥ 4 mmol/L (154 mg/dL) if not on a statin • LDL-C level ≥ 2.5 mmol/L (96 mg/dL) if on a statin prior to presentation • Non-HDL-C ≥ 4.6 mmol/L (177 mg/dL) if LDL-C not available	Do not wish to undergo research based genetic analysis
Admitted to an acute cardiac unit at VGH or SPH with either: • A ST elevation myocardial infarction (STEMI) • A non-ST elevation myocardial infarction (NSTEMI)	

Table 2
Study endpoints for the ACCURATE study.

	Endpoints	Details
Primary	Number of patients with a new diagnosis of FH	Diagnosis based on: 1. Presence of an FH-causing DNA variant, or 2. Clinical diagnosis of FH based on Dutch Lipid Clinic Network score or Canadian Definition of FH
Secondary	Proportion of patients in whom lipid-lowering medication intensified, as defined by an increase the dose of statin, or the addition of a non-statin lipid-lowering medication, in the first year after ACS	Non-statin medications include: 1. Ezetimibe 2. Monoclonal antibodies against PCSK9 (evolocumab or alirocumab) 3. Inclisiran 4. Fibrate 5. Bile acid resin
	Lowest LDL-cholesterol (LDL-C) level achieved in the first year after ACS	
	Proportion of patients who achieve guideline recommended lipid targets in the first year after ACS	1. Canadian Cardiovascular Society Guidelines: LDL-C < 1.8 mmol/L (<69 mg/dL) 2. European Society of Cardiology Guidelines: ≥50% LDL-C reduction from baseline and LDL-C < 1.4 mmol/L (<54 mg/dL)
Exploratory Endpoint	Rate of recurrent cardiovascular event in the first year after ACS	1. Unstable angina 2. Myocardial infarction 3. Urgent coronary revascularization 4. Death

of-care. Cohort 2 (Active testing group) will be recruited from time 6 to 18 months and will undergo research-based genetic testing for FH with results returned to the patients' specialist and primary care physicians. Patients will follow up with their physicians according to the usual standard-of-care, and further treatment will be left to the discretion of the treating physicians.

The principal objective of the ACCURATE study is to investigate the ability of real-time genetic testing to identify FH among patients admitted to the acute cardiac care setting with an ACS and to understand the impact of establishing a genetic diagnosis on the behaviour of treating physicians, medication use, and achieved lipid levels. The specific objectives are:

1. To assess the feasibility of real-time genetic diagnosis of FH for patients admitted to hospital with an ACS.
2. To determine the diagnostic yield of research-based genetic identification of FH among patients with ACS.
3. To assess the effect of genetic identification of FH on patient care and outcomes, compared to standard practice.

2.2. Patient recruitment and inclusion/exclusion criteria

Inclusion and exclusion criteria are shown in Table 1. Briefly, patients will be eligible for the study if they are 60 years of age or less, have an LDL-C > 4 mmol/L (154 mg/dl) or non-HDL-C > 4.6 mmol/L (177 mg/dL), or >2.5 mmol/L (96 mg/dl) if on a statin for greater than or equal to one month prior to presentation, and are admitted to an acute cardiac unit with a diagnosis of ST-elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI). Because LDL-C levels may be transiently reduced during an ACS [12], or may not always be measured in patients admitted with an ACS, the highest LDL-C or non-HDL-C level in the 12 months preceding the date of admission to hospital will also be used to determine eligibility. The diagnosis of STEMI and NSTEMI will be based on recommendations from the Fourth Universal Definition of Myocardial Infarction consensus guidelines [13]. Patients are excluded from the study if they are unable or unwilling to provide consent or do not wish to undergo research-based genetic analysis. Assessment of physical stigmata of FH will not be protocolized, but will be recorded when noted in consultation reports.

2.3. Study endpoints

Study endpoints are shown in Table 2. The primary endpoint of the study will be the number of patients with a new diagnosis of FH, as defined by identification of a pathogenic or likely pathogenic DNA variant (Fig. 2), or a clinical diagnosis of FH based on the Dutch Lipid Clinic Network criteria [7] or the Canadian Definition of FH [14]. Secondary endpoints will include (1) the proportion of patients who undergo intensification of lipid-lowering therapy in the first year after ACS (defined as up-titration of statin dose or addition of non-statin lipid-lowering therapy); (2) the lowest LDL-C level achieved in the first year after ACS; and (3) the proportion of patients who reached guideline recommended lipid targets, defined as LDL-C < 1.8 mmol/L (69 mg/dL) [15,16]. Exploratory end-points will include the rate of occurrence of cardiovascular events in the first year after the qualifying ACS, defined as hospitalization for unstable angina, myocardial infarction, urgent coronary revascularization, or death. Adjudication of study end-points will be completed by the study personnel, blinded to the testing allocation, through review of the patients' electronic medical records. The occurrence of primary and secondary endpoints will be compared between study participants in Cohorts 1 and 2 using *t*-tests for continuous variables and chi-squared tests for categorical variables. Within Cohort 2, we will additionally compare endpoints for patients with and without a diagnosis of FH.

2.4. Genetic diagnosis for FH

2.4.1. DNA sequencing

Saliva samples will be collected from patients in Cohort 2 using the Genotek saliva DNA collection kit. DNA will be extracted from the saliva samples according to the manufacturer's instructions and quantified using the Quant-iT PicoGreen assay (Life Technologies). Targeted sequencing will be performed on the extracted DNA following previously published methods [17]. In brief, library preparation will be performed with either the Tru-Seq Custom Amplicon Kit (Illumina, San Diego, California) or the AmpliSeq Custom Amplicon Kit (Illumina) to target FH specific candidate gene regions. Sequencing of the samples will be performed on the Illumina MiSeq instrument in 2 × 151 bp mode using the 300-cycles MiSeq Reagent v2 Kit (Illumina).

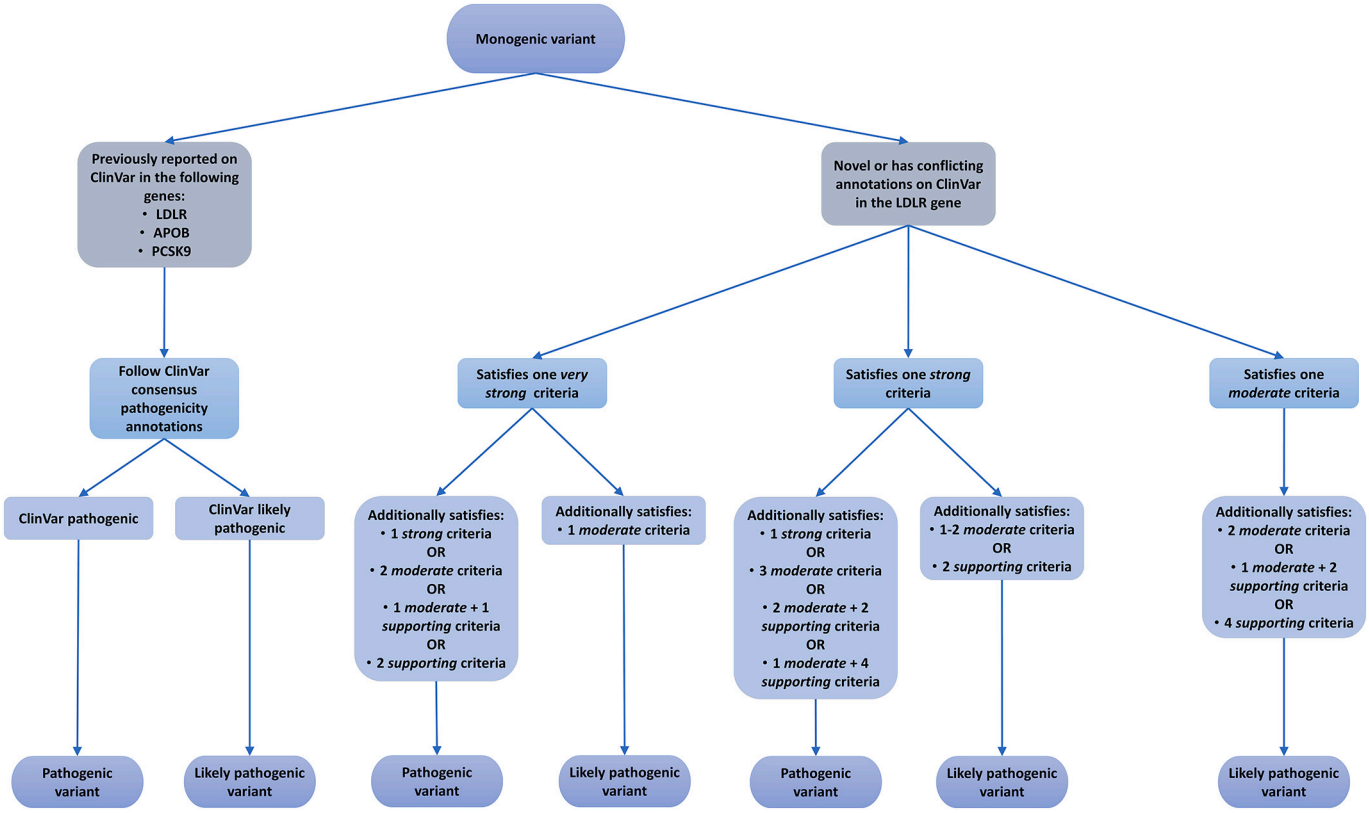

Fig. 2. Workflow for monogenic variant pathogenicity determination in the ACCURATE study. All rules follow the American College of Medical Genetics and Genomics (ACMG) recommendations. Very strong, strong, moderate and supporting criteria are in accordance with the Clinical Genome Resource (ClinGen) FH Variant Curation Expert Panel guidelines and are summarized in Supplementary Table 1.

2.4.2. *Determination of variant pathogenicity*

The FASTQ files will be aligned to the hg19 reference genome using the Local Run Manager Off-Instrument Software (Illumina) to generate VCF and BAM files, which will be uploaded to VarSeq Version 2.0.2 and VarSeq CNV Caller (Golden Helix, Bozeman, Montana) for single nucleotide variant (SNV), short indel and structural variant (SV) annotation of the *LDLR*, *APOB* and *PCSK9* genes. Variant calling and filtering will follow previously published methods [17]. For SNVs and indels, variants will be filtered to only include calls with a quality score > 30 and read depth > 15. For SVs, coverage data from the samples will be analyzed against a set of matched controls. This analysis will output ratio and *Z*-score values, which provide evidence for the presence of deletions or duplications in the samples. For the purposes of this study, a ratio ≤ 0.7 and $p < 0.01$ will be used to indicate a probable deletion, while a ratio ≥ 1.20 and $p < 0.01$ will be considered a probable duplication.

Monogenic variant pathogenicity will be assigned in accordance with the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines [18]. The workflow for determining variant pathogenicity for the purposes of the ACCURATE study is summarized in Fig. 2. For previously reported variants in the *LDLR*, *APOB* and *PCSK9* genes, pathogenicity will be assigned as annotated for FH in ClinVar. For novel *LDLR* variants or *LDLR* variants with conflicting ClinVar annotations, pathogenicity will be assigned in accordance with the Clinical Genome Resource (ClinGen) FH Variant Curation Expert Panel guidelines [19]. In brief, *very strong*, *strong*, *moderate*, and *supporting* criteria (see Supplementary Table 1) will be determined to classify variants as "pathogenic" or "likely pathogenic" [18]. Rare or novel variants in the *LDLR* gene will be assigned "pathogenic" if they are: (1) nonsense or frameshift variants which occur amino-terminal of amino acid 830; (2) variants that alter the AG/GT nucleotide sequence at splice junctions leading to disrupted splicing; (3) full gene or single/multi-exon deletions; or (4) tandem duplications leading to frameshift in exons 1–17. Novel missense variants occurring at the same codon as a previously identified pathogenic variant will also be assigned "pathogenic" or "likely pathogenic" with consideration of additional criteria, such as minor allele frequency, variant prevalence in unrelated FH cases, and *in silico* prediction scores. Finally, missense variants located in exon 4, missense variants in any one of the 60 highly conserved cysteine residues in the *LDLR* gene, and small duplications, deletions and insertions that preserve the reading frame and satisfy additional pathogenic criteria will also be assigned "likely pathogenic" for this study.

In addition to the analysis of monogenic variants, a weighted LDL-C polygenic risk score (PRS) will also be calculated for all patients. The LDL-C PRS will comprise of 28 SNVs from the Global Lipid Genetics Consortium genome-wide association study [17,20]. The LDL-C PRS will be calculated following previously published methods [17]. The PRS will be expressed as a percentile ranking within matched population reference values. A PRS >80th percentile without a corresponding monogenic FH variant will be classified as a diagnosis of polygenic hypercholesterolemia [21].

2.5. *Delivery of genetic test reports to providers and follow-up*

2.5.1. *Genetic test reports*

Genetic test reports will be generated using the VarSeq Clinical workflow (Golden Helix) and returned to the patient's treating physicians within a targeted timeframe of one month from DNA sample collection. Test reports will indicate that targeted sequencing and analysis was performed on the *LDLR*, *APOB* and *PCSK9* genes, as well as the 28 SNV loci for PRS calculations. For monogenic variants detected, the reports will also contain variant information and a summary of the evidence supporting pathogenicity. An interpretation of the analysis

results will be included to specify a positive or negative finding for monogenic FH. The LDL-C PRS will also be reported.

2.5.2. Follow-up

There will be no post-discharge study visits. Patients will follow up with their treating physicians as clinically indicated, and all treatment decisions will be at the discretion of the treating physician.

2.6. Sample size considerations

Based on current patient volumes at the two study sites, we expect to recruit approximately 250 patients to the study over the 18-month timeframe. With this sample size, we can calculate the achievable precision for our primary and secondary endpoints (Table 3). According to previous population estimates [4], we anticipate ~10% of the patients meeting inclusion criteria will have genetically implicated FH, resulting in ~25 patients with FH recruited to the study. Based on the desired confidence interval of 95%, the level of precision we are able to achieve for the primary endpoint (number of patients with a new genetic diagnosis of FH) is approximately ±3.7%. For the first secondary endpoint (proportion of patients in whom lipid lowering therapy intensified in the first year after ACS), we predict the sample proportion in the patient population to be approximately 15%. We, therefore, anticipate our level of precision for the first secondary endpoint to be ±4.4%. For the second secondary endpoint (the lowest LDL-C level achieved in the first year after ACS), the level of precision can be calculated based on previously reported LDL-C level population variance in ACS patients [22]. Again, setting a desired confidence interval of 95%, the level of precision we are able to achieve for LDL-C measurements is approximately ±0.16 mmol/L. Finally, for the third secondary endpoint (the proportion of patients who achieve guideline recommended lipid targets in the first year after ACS), we predict the sample proportion in the patient population to be approximately 50%, which sets the level of precision for this endpoint at ±6.2%.

2.7. Data management

Data collected in the ACCURATE study will be stored in a secure REDCap database. Access to data will be based on hierarchical authorization. Requests to access de-identified data will be submitted to the Principal Investigator of the study for consideration and approval. Biological samples will be stored in a 24-h monitored, secured -80 °C freezer facility at the Centre for Heart Lung Innovation, University of British Columbia.

Table 3
Sample size considerations and precision calculations for the ACCURATE study. Precision calculations for the primary and secondary endpoints were included. Precision is represented here as a margin of error, which is defined as half the width of the confidence interval.

Endpoint	Parameters	Precision
Proportion of patients with a new genetic diagnosis of FH	n = 250 CI = 95% Sp = 10%	±0.037
Proportion of patients in whom lipid lowering therapy is intensified in the first year after ACS	n = 250 CI = 95% Sp = 15%	±0.044
Lowest LDL-cholesterol (LDL-C) level achieved in the first year after ACS	n = 250 CI = 95% SD = 1.28 mmol/L (49 mg/dL)	±0.16 mmol/L (6.2 mg/dL)
Proportion of patients who achieve guideline recommended lipid targets	n = 250 CI = 95% Sp = 50%	±0.062

Abbreviations: *n*, sample size; *CI*, expected confidence interval; *Sp*, sample proportion; *SD*, standard deviation of the population.

2.8. Trial registration

ACCURATE is registered at clinicaltrial.gov (Identifier: NCT05218005).

3. Discussion

The ACCURATE study will be, to our knowledge, the first prospective clinical trial of genetic testing of FH in patients hospitalized with ACS and will answer the question of whether clinical implementation of genetic testing within the acute cardiac care setting improves the early diagnosis and treatment of FH.

Due to the high prevalence of FH in ACS patients under the age of 60, genetic diagnosis in this population is anticipated to have a high diagnostic yield. A secondary endpoint in the ACCURATE study will be to determine the extent to which identification of FH leads to treatment intensification such as the addition of non-statin lipid-lowering therapies including ezetimibe and inhibitors of PCSK9. In this respect, it is anticipated that a diagnosis of FH may facilitate the intensification of treatment of these patients, as the reimbursement for PCSK9 inhibitors is dependent in some instances on a clinical diagnosis of FH. One of the main advantages of diagnosing FH is to enable cascade screening of family members which can identify new cases who may be eligible for primary preventative therapies [23]. A genetic diagnosis of FH may also have personal utility for index cases and improve medication adherence [24].

Several observational studies have investigated the prevalence of FH in ACS (Table 4) [25–34]. To our knowledge, ACCURATE is the first trial to prospectively evaluate the clinical utility of genetic testing for FH in the acute cardiac care setting. ACCURATE will therefore provide important new data regarding the clinical utility of genetic testing in this setting. An important future direction of ACCURATE will be to conduct cascade testing of the first-degree relatives of index cases of FH detected in this study. Cascade testing would be expected to identify additional cases of FH who have not yet manifested ASCVD, and would benefit from primary preventative therapies [23].

3.1. Limitations

There are important limitations to this study that merit consideration. For reasons of cost and complexity, allocation to genetic testing or standard-of-care will be sequential and not-randomized, and group allocation will not be blinded. It is possible that the groups of patients allocated to genetic testing or standard-of-care may differ in certain measured or unmeasured characteristics, introducing an element of selection bias. However, by recruiting patients from the same site and using the same inclusion and exclusion criteria, it is expected that the groups will be well-balanced in terms of key characteristics. The main endpoints are rates of diagnosis of FH and treatment efficacy; the study will lack statistical power to investigate a difference in the occurrence of clinical endpoints. However, if a difference in treatment intensity is demonstrated, the predicted effect on clinical end-points could be extrapolated, and this could be specifically assessed in a subsequent, larger trial. In addition, the study will use a research-based assay for genetic identification of FH and not an approved clinical diagnostic test. This relates to the fact that a clinical-approved laboratory test for FH is not available in British Columbia. Nonetheless, the research-based assay has been shown to be sensitive and specific [35]. In addition, a strength of ACCURATE will be the use of the most updated ClinGen guidelines for annotation of pathogenic FH variants.

3.2. Sub-studies and future directions

Future sub-studies will include comparing treatment and outcomes for patients with a clinical *versus* genetic diagnosis of FH; investigating health care provider perspectives, attitudes, and behaviours after

Table 4
Comparison of studies investigating familial hypercholesterolemia among patients with an acute coronary syndrome.

Study	Inclusion	Design	Sample size	Acute setting	Genetic investigation
Yudi et al. 2012 [32]	Males ≤55 and females ≤60 years of age admitted with ACS or stable CAD	Retrospective	210	Yes	No
Wald et al., 2015 [31]	Patients ≤50 years of age with STEMI or NSTEMI	Retrospective	231	Yes	Yes
Nanchen et al., 2015 [34]	Patients admitted with ACS from 2009 to 2014 with available values for total cholesterol, HDL-C and triglycerides	Prospective	4778	Yes	No
Pang et al., 2015 [30]	Patients less than 60 years of age admitted to the CCU with current or prior history of CAD defined as ACS, coronary revascularization, or angina	Prospective	175	Yes	No
EXPLORE-J [27]	Patients ≥20 years of age admitted with ACS	Prospective	1944	Yes	No
Amor-Salamanca et al., 2017 [33]	Patients with ACS ≤ 65 years of age with LDL-C ≥ 160 mg/dl	Retrospective	103	Yes	Yes
GenTLe-FH [26]	Clinically diagnosed FH with CHD greater than 15 years of age	Waiting list controlled open-label study protocol	100	No	Yes
Benedek et al., 2018 [28]	Patients with a diagnosis of ACS up to 5 years prior to study enrolment meeting indicated elevated lipid requirement	Retrospective	116	No	Yes
Al-Rasadi et al., 2018 [29]	Patients greater than 18 years of age admitted with ACS	Prospective	3224	Yes	No
YOUNG-MI [25]	Patients ≤50 years of age admitted for ACS with available LDL-C levels	Retrospective	1996	No	No
ACCURATE	Patients admitted with ACS <60 years of age	Prospective, non-randomized control trial	250	Yes	Yes

Abbreviations: FH, familial hypercholesterolemia; CAD, coronary artery disease; NSTEMI, non-ST elevated myocardial infarction; STEMI, ST elevated myocardial infarction; ACS, acute coronary syndrome; HDL—C, high-density lipoprotein C; CCU, coronary care unit; LDL-C, low-density lipoprotein C; CHD, coronary heart disease.

receiving genetic analysis of patients with suspected FH; optimizing health care provider education regarding the usage of genetics in diagnosing FH; and analysis of the cost-effectiveness of genetic testing of FH in the healthcare system.

4. Conclusion

FH is a highly prevalent, but significantly underdiagnosed condition that can lead to early onset ASCVD. The ACCURATE study will determine the clinical utility of genetic testing of FH among patients presenting with an ACS. These results are expected to provide much-needed evidence supporting the clinical implementation of genetic testing of FH in the acute cardiac care setting.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100097.

Funding

ACCURATE is funded by a GeneSolve award from Genome British Columbia, and by the Vancouver Coastal Health Research Institute. The funders have no role in the design or conduct of the trial.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S.O. Beheshti, C.M. Madsen, A. Varbo, B.G. Nordestgaard, Worldwide prevalence of familial hypercholesterolemia: meta-analyses of 11 million subjects, J. Am. Coll. Cardiol. 75 (20) (2020) 2553–2566.
[2] B.G. Nordestgaard, M.J. Chapman, S.E. Humphries, H.N. Ginsberg, L. Masana, O. S. Descamps, et al., Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European atherosclerosis society, Eur. Heart J. 34 (45) (2013), 3478-90a.
[3] J.K. Morris, D.S. Wald, N.J. Wald, The evaluation of cascade testing for familial hypercholesterolemia, Am. J. Med. Genet. A 158A (1) (2012) 78–84.
[4] A.I. Kramer, M. Trinder, L.R. Brunham, Estimating the prevalence of familial hypercholesterolemia in acute coronary syndrome: a systematic review and meta-analysis, Can. J. Cardiol. 35 (10) (2019) 1322–1331.
[5] B. Gencer, F. Mach, S.A. Murphy, G.M. De Ferrari, K. Huber, B.S. Lewis, et al., Efficacy of evolocumab on cardiovascular outcomes in patients with recent myocardial infarction, JAMA Cardiol. 5 (8) (2020) 952.
[6] L.R. Brunham, I. Ruel, S. Aljenedil, J.B. Riviere, A. Baass, J.V. Tu, et al., Canadian cardiovascular society position statement on familial hypercholesterolemia: update 2018, Can. J. Cardiol. 34 (12) (2018) 1553–1563.
[7] M.A. Austin, C.M. Hutter, R.L. Zimmern, S.E. Humphries, Familial hypercholesterolemia and coronary heart disease: a HuGE association review, Am. J. Epidemiol. 160 (5) (2004) 421–429.
[8] Group SSCobotSBR, Risk of fatal coronary heart disease in familial hypercholesterolaemia, BMJ 303 (6807) (1991) 893–896.
[9] National Institute for Health and Care Excellence, Familial Hypercholesterolaemia: Identification and Management, 2008.
[10] A.C. Sturm, J.W. Knowles, S.S. Gidding, Z.S. Ahmad, C.D. Ahmed, C.M. Ballantyne, et al., Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel, J. Am. Coll. Cardiol. 72 (6) (2018) 662–680.
[11] B.G. Nordestgaard, M. Benn, Genetic testing for familial hypercholesterolaemia is essential in individuals with high LDL cholesterol: who does it in the world? Eur. Heart J. 38 (20) (2017) 1580–1583.
[12] B. Pitt, J. Loscalzo, J. Ycas, J.S. Raichlen, Lipid levels after acute coronary syndromes, J. Am. Coll. Cardiol. 51 (15) (2008) 1440–1445.
[13] K. Thygesen, J.S. Alpert, A.S. Jaffe, M.L. Simoons, B.R. Chaitman, H.D. White, et al., Third universal definition of myocardial infarction, J. Am. Coll. Cardiol. 60 (16) (2012) 1581–1598.
[14] I. Ruel, D. Brisson, S. Aljenedil, Z. Awan, A. Baass, A. Bélanger, et al., Simplified Canadian definition for familial hypercholesterolemia, Can. J. Cardiol. 34 (9) (2018) 1210–1214.
[15] G.J. Pearson, G. Thanassoulis, T.J. Anderson, A.R. Barry, P. Couture, N. Dayan, et al., 2021 Canadian cardiovascular society guidelines for the Management of Dyslipidemia for the prevention of cardiovascular disease in adults, Can. J. Cardiol. 37 (8) (2021) 1129–1150.
[16] F. Mach, C. Baigent, A.L. Catapano, K.C. Koskinas, M. Casula, L. Badimon, et al., 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk, Eur. Heart J. 41 (1) (2020) 111–188.
[17] M. Trinder, X. Li, M.L. DeCastro, L. Cermakova, S. Sadananda, L.M. Jackson, et al., Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia, J. Am. Coll. Cardiol. 74 (4) (2019) 512–522.
[18] C.S. Richards, S. Bale, D.B. Bellissimo, S. Das, W.W. Grody, M.R. Hegde, et al., ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007, Genet. Med. 10 (4) (2008) 294–300.
[19] J.R. Chora, M.A. Iacocca, L. Tichy, H. Wand, C.L. Kurtz, H. Zimmermann, et al., The clinical genome resource (ClinGen) familial hypercholesterolemia variant curation expert panel consensus guidelines for LDLR variant classification, Genet. Med. 24 (2) (2022) 293–306.
[20] C.J. Willer, E.M. Schmidt, S. Sengupta, G.M. Peloso, S. Gustafsson, S. Kanoni, et al., Discovery and refinement of loci associated with lipid levels, Nat. Genet. 45 (11) (2013) 1274–1283.
[21] M. Trinder, M. Paquette, L. Cermakova, M.R. Ban, R. Hegele, A. Baass, Polygenic contribution to low-density lipoprotein cholesterol levels and cardiovascular risk in monogenic familial hypercholesterolemia, Circ. Genomic Precis. Med. 3 (5) (2020) 515–523.

[22] C.P. Cannon, M.A. Blazing, R.P. Giugliano, A. McCagg, J.A. White, P. Theroux, et al., Ezetimibe added to statin therapy after acute coronary syndromes, N. Engl. J. Med. 372 (25) (2015) 2387–2397.
[23] J.W. Knowles, D.J. Rader, M.J. Khoury, Cascade screening for familial hypercholesterolemia and the use of genetic testing, JAMA 318 (4) (2017) 381–382.
[24] M. Marchand, V. Chen, M. Trinder, L. Cermakova, L.R. Brunham, Patient perspectives regarding genetic testing for familial hypercholesterolemia, CJC Open 3 (5) (2021) 557–564.
[25] A. Singh, A. Gupta, B.L. Collins, A. Qamar, K.L. Monda, D. Biery, et al., Familial hypercholesterolemia among young adults with myocardial infarction, J. Am. Coll. Cardiol. 73 (19) (2019) 2439–2450.
[26] A. Nomura, H. Tada, H. Okada, A. Nohara, H. Ishikawa, K. Yoshimura, et al., Impact of genetic testing on low-density lipoprotein cholesterol in patients with familial hypercholesterolemia (GenTLe-FH): a randomised waiting list controlled open-label study protocol, BMJ Open 8 (12) (2018), e023636.
[27] M. Harada-Shiba, J. Ako, H. Arai, A. Hirayama, Y. Murakami, A. Nohara, et al., Prevalence of familial hypercholesterolemia in patients with acute coronary syndrome in Japan: results of the EXPLORE-J study, Atherosclerosis 277 (2018) 362–368.
[28] P. Benedek, M. Eriksson, K. Duvefelt, A. Freyschuss, M. Frick, P. Lundman, et al., Genetic testing for familial hypercholesterolemia among survivors of acute coronary syndrome, J. Intern. Med. 284 (6) (2018) 674–684.
[29] K. Al-Rasadi, I. Al-Zakwani, A.A. Alsheikh-Ali, W. Almahmeed, W. Rashed, M. Ridha, et al., Prevalence, management, and outcomes of familial hypercholesterolemia in patients with acute coronary syndromes in the Arabian gulf, J. Clin. Lipidol. 12 (3) (2018) 685–692 e2.
[30] J. Pang, E.B. Poulter, D.A. Bell, T.R. Bates, V.L. Jefferson, G.S. Hillis, et al., Frequency of familial hypercholesterolemia in patients with early-onset coronary artery disease admitted to a coronary care unit, J. Clin. Lipidol. 9 (5) (2015) 703–708.
[31] D.S. Wald, F.A. Bangash, J.P. Bestwick, Prevalence of DNA-confirmed familial hypercholesterolaemia in young patients with myocardial infarction, Eur. J. Intern. Med. 26 (2) (2015) 127–130.
[32] M. Yudi, L. Omera, N. McCubbery, S. Dick, R. Jayasinghe, I. Hamilton-Craig, Suboptimal consideration and management of potential familial hypercholesterolaemia in patients with suspected premature coronary artery disease, Singap. Med. J. 53 (3) (2012) 174–178.
[33] A. Amor-Salamanca, S. Castillo, E. Gonzalez-Vioque, F. Dominguez, L. Quintana, C. Lluis-Ganella, et al., Genetically confirmed familial hypercholesterolemia in patients with acute coronary syndrome, J. Am. Coll. Cardiol. 70 (14) (2017) 1732–1740.
[34] D. Nanchen, B. Gencer, R. Auer, L. Raber, G.G. Stefanini, R. Klingenberg, et al., Prevalence and management of familial hypercholesterolaemia in patients with acute coronary syndromes, Eur. Heart J. 36 (36) (2015) 2438–2445.
[35] S.N. Sadananda, J.N. Foo, M.T. Toh, L. Cermakova, L. Trigueros-Motos, T. Chan, et al., Targeted next-generation sequencing to diagnose disorders of HDL cholesterol, J. Lipid Res. 56 (10) (2015) 1993–2001.