Effects of artificial intelligence-Supported Automated NutRiTional Intervention on LDL cholesterol Control in Patients with Familial Hypercholesterolaemia (iSTART-FH): protocol for a randomised controlled trial

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ABSTRACT

Introduction Familial hypercholesterolaemia (FH) is an autosomal dominant inherited genetic disease that has an extremely elevated cardiovascular risk because of their significantly elevated low-density lipoprotein (LDL) cholesterol. Nutritional intervention is needed in improving LDL cholesterol control in patients with FH but requires a considerable burden in manpower. Artificial intelligence (AI)-supported mobile nutrition counselling is more effective in reducing LDL cholesterol than the in-person, face-to-face method in terms of improving LDL cholesterol control in patients with FH.

Methods and analysis This is a single-centre, unblinded, cross-over, randomised controlled study comparing the efficacy of AI-supported automated nutrition therapy with that of conventional human nutrition counselling in patients with FH. Patients with FH are recruited and randomly assigned to AI-supported nutrition counselling (n=30) and to face-to-face nutrition counselling (n=30). We are using an Asken, a mobile application that has been specially modified for this study so that it follows the recommendations by the Japan Atherosclerosis Society. We started patient recruitment on 1 September 2020, and is scheduled to continue until 31 December 2022.

Ethics and dissemination This study is being conducted in compliance with the Declaration of Helsinki, the Ethical Guidelines for Medical and Health Research Involving Human Subjects, and all other applicable laws and guidelines in Japan. The study protocol was approved by the Institutional Review Board of Kanazawa University on 13 April 2020 (IRB no. 2623-3). We will disseminate the final results at international conferences and in a peer-reviewed journal.

Strengths and limitations of this study

- Most of the patients who will be included into this study are fully assessed regarding familial hypercholesterolaemia-associated phenotypes, including cardiovascular disease and genetics.
- This study is conducted in a single-centre manner.
- This is not a double-blind study.
- We will not record their physical activity in this study, which may affect the results.
METHODS AND ANALYSIS

Overall study design

This is a single-centre, unblinded, cross-over, randomised controlled study, comparing the efficacy of AI-supported automated nutrition counselling with that of conventional human nutrition counselling in patients with FH. The study protocol was approved by the Institutional Review Board of Kanazawa University on 13 April 2020 (IRB no. 2623-3); all recruited patients are required to provide written informed consent (online supplemental material). We started patient recruitment on 1 September 2020, and is scheduled to continue until 31 December 2022.

Figure 1 shows the scheme of this study, and table 1 outlines the overall follow-up schedule. The primary outcome of this study is the absolute change of LDL cholesterol at 12 months from baseline. The secondary outcomes are as follows: the absolute change/the per cent change of fasting glucose at 12 months from baseline, cost during the study period, the absolute change/the per cent change of blood pressure at 12 months from baseline, the absolute change/the per cent change of serum lipids (total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol) at 12 months from baseline, the absolute change/the per cent change of urine albumin at 12 months from baseline, number of new-onset diabetes, changes in lipid-lowering therapies that occurred during the study period, frequency of use of the smartphone app, and the absolute/per cent LDL cholesterol change due to the change of nutritional intake.

Basic variables include gender, height, body weight. Complications include new onset of diabetes, elevation of LDL cholesterol by 20% (from baseline), or any unexpected complications that are clinically important. Laboratory data include blood counts, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, lipoprotein (a), apolipoproteins, plasma glucose, hemoglobin A1c (HbA1c), aspartate aminotransferase, alanine
transaminase, γ-glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, blood urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, C reactive protein, insulin, renin, aldosterone, brain natriuretic peptide (BNP), urinalysis.

**Study participants**

Patients with clinically diagnosed FH from September 2020 to December 2022 will be recruited, and participants will be followed for 2 years. Of note, only participants fulfilling all of the inclusion criteria will be enrolled in this study (box 1), and those with any of the exclusion criteria were excluded from this trial (box 2). On obtaining consent, the first copy of the consent form will be kept in the hospital, and the other part will be kept by the patient and will not be collected after the trial is completed. Furthermore, all participants will be informed that their medical care will not be affected if they refused to enrol in the trial and that they will be free to withdraw their consent at any time of the study period, at their discretion.

**Randomisation**

Patients are randomised into two groups stratified by age and gender (1:1 allocation ratio) using Research Electronic Data Capture.

**Patient and public involvement**

Patients will not be invited to comment on the study design and will not be consulted to develop patient relevant outcomes or interpret the results. Patients will not be invited to contribute to the writing or editing of this document for readability or accuracy.

**AI-supported nutrition counselling and conventional counselling**

The mobile phone app used for this study is called ‘Asken’ and is one of the most popular Japanese apps for behaviour change among individuals aspiring to lose weight. The criteria of its nutritional feedback system have been specially modified for this study so that it follows the recommendations set by the Japan Atherosclerosis Society. An example of this technology can be seen in figure 2: it can identify each menu item and serving amount. After confirmation by the patient, the app calculates approximate energy and nutrient intakes. Following these processes, Asken summarises daily dietary intake to generate advice on changes in dietary habits.\(^{15,16}\) Following these processes, Asken calculates the score evaluating their dietary intake with a chart, and a Japanese character named as ‘Miki’ delivers messages

**Box 1 Inclusion criteria**

The patients are included on the basis of the following inclusion criteria:

1. Diagnosed with familial hypercholesterolaemia per the criteria of the Japan Atherosclerosis Society.
2. Patients who can provide written informed consent.
3. LDL-C ≥100 mg/dL.
4. Age ≥20 years.
5. Patients who can use smartphone app.

**Box 2 Exclusion criteria**

The patients are excluded on the basis of either of the following criteria:

1. Patients whose doctors consider him/her inappropriate to participate.
2. Patients with diabetes.
3. Patients with malignant hypertension or secondary hypertension.
4. Pregnant women or those who are expecting to get pregnant.
5. Renal dysfunction (eGFR <45 mL/min/1.73 m\(^2\)).
6. Severe liver dysfunction.
7. Allergy and/or under steroid therapy.
8. Pancreatitis (active or history).
9. Under treatment of malignancies.

| Variables                  | Preobservation period | Intervention period | Cross-over period | Intervention period |
|----------------------------|-----------------------|---------------------|-------------------|---------------------|
|                            | Day -91 ~ -1          | Day 0               | 3 months          | 6 months            | 9 months            | 1 year | Per months |
| Visit 1                    |                       | Visit 2             | Visit 3           | Visit 4             | Visit 5             | Visit 6 | Visit       |
| Informed consent           | ○                     |                     |                   |                     |                     |        |             |
| Intervention               |                       |                     |                   |                     |                     |        |             |
| Complications              |                       | ○                   | ○                 | ○                   | ○                   | ○      |             |
| Clinical testing           |                       |                     |                   |                     |                     |        |             |
| Body weight                | ○                     | ○                   | ○                 | ○                   | ○                   | ○      |             |
| Blood pressure             | ○                     | ○                   | ○                 | ○                   | ○                   |          |
| Laboratory data            | ○                     | ○                   | ○                 | ○                   | ○                   |          |
| Urinary test               | ○                     | ○                   | ○                 | ○                   |                      |          |
| Evaluation of diet         |                       |                     |                   |                     |                     |        |             |
| Sending pictures of diet   |                       |                     |                   |                     |                     |        |             |
| through smartphone app     |                       |                     |                   |                     |                     |        |             |

Table 1 Assessment and evaluation schedule of this study
that are composed individually from more than 200,000 different patterns. (figure 3). This app has been validated in terms of intakes of energy and nutrients.16

Conventional nutritional counselling provides the fundamental points of information in-person regarding recommended diet for patients with FH: (1) saturated fatty acid of <7%, (2) avoidance of trans-fatty acids and (3) cholesterol intake of <200 mg/day.

For both groups, conventional nutritional counselling is provided as the initial counselling.

Genetic testing
We intend to sequence exons of four FH-related genes (LDLR, PCSK9, APOB and LDLRAP1) as well as other genes associated with Mendelian lipid disorders, such as adenosine triphosphate (ATP)-binding cassette subfamily G member 5 (ABCG5) and ATP-binding cassette subfamily G member 8 (ABCG8) using the Illumina MiSeq system. The variant is defined as causal when it fulfills either of the following criteria: (A) it is registered as pathogenic/likely pathogenic in the ClinVar database; (B) minor allele frequency is <1% in the East Asian population with (1) protein-truncating variants (nonsense, canonical splice sites or frameshift) and (2) missense variants in the LDLR gene that five in silico damaging scores (SIFT, PolyPhen-2 HDIV, PolyPhen-2 HVAR, MutationTaster2, LRT) all predicted as pathogenic; (C) missense variants reported as pathogenic in the Japanese population (PCSK9 p.Val4Ile and p.Glu32Lys) and (4) eXome-Hidden Markov Model software predicted as copy number variations in the LDLR gene (large duplication/ large deletion). Details are described elsewhere.12

Data collection
Data collection will be conducted by the attending physicians or the research assistants under the supervision of the clinicians responsible for this study at each participating hospital. The proposed time frame for data collection after the initial enrolment is shown in table 1. Research monitoring will be conducted by the Innovative Clinical Research Center, Kanazawa University. It ensures the compliance with the study protocol and the record of adverse events, including cardiovascular outcomes, such as coronary artery disease and stroke in the case report forms (CRFs).

Outcomes
The primary outcome of this study is the absolute change of LDL cholesterol at 12 months from baseline. The secondary outcomes are the following: the absolute change/the per cent change of fasting glucose at 12 months from baseline, cost during the study period, the absolute change/the per cent change of blood pressure at 12 months from baseline, the absolute change/the per cent change of serum lipids (total cholesterol, triglycerides and HDL cholesterol) at 12 months from baseline, the absolute change/the per
cent change of urine albumin at 12 months from baseline, number of new-onset diabetes, changes in lipid-lowering therapies that occurred during the study period, frequency of use of the smartphone app, and the absolute/per cent LDL cholesterol change due to the change of nutritional intake.

Data collection schedule
Table 1 lists the overall data collection schedule for this study. Follow-up visits will be conducted in outpatient clinics at the Kanazawa University Hospital. Data will be collected at any time point when any events occurred.

Concomitant medication
LDL cholesterol lowering therapies and other intakes of any supplementations are not changed during the study period. If this is inevitable, then a full description of the change and the reason and timing are recorded in the CRF.

Sample sizes
The primary endpoint of this study is the absolute change of LDL cholesterol at 12 months from baseline. Considering the degree of reduction in LDL cholesterol in previous studies through conventional interventions, the mean change in LDL cholesterol was expected to be 30 mg/dL with an SD of 40 mg/dL. We anticipate that LDL cholesterol reduction will be unchanged in an AI-supported nutrition counselling group, whereas LDL cholesterol will return to the baseline in a conventional counselling group. At a significance level of 0.05 and a detection power of 80%, the number of cases per group necessary to reach significant difference in change in LDL cholesterol between two groups is calculated to be 28 cases. Assuming a few dropouts, the target number of cases for each group is 30 cases, with a total of 60 participants in this study.

Statistical analysis
The primary aim is to confirm that AI-supported, fully automated nutritional intervention is superior to nutritional counselling in-person in terms of LDL cholesterol reduction during a 12-month period. Student’s t-test is used to compare the two groups for the absolute change in LDL cholesterol. The changes in secondary continuous outcomes are also analysed using the t-test, Mann-Whitney U-test or Fisher’s exact test. Analyses are performed using R software V.3.6.4 (The R Project for Statistical Computing, Vienna, Austria). All tests are conducted as two-sided α=0.05, and 95% CIs are calculated.

DISCUSSION
The SupporTed Automated NutRiTional Intervention on LDL Cholesterol Control in Patients with FH (iSTART-FH) study is a single-centre, unblinded, crossover, randomised controlled study aimed at comparing the efficacy of AI-supported automated nutritional counselling with that of conventional human nutritional counselling in patients with FH. The iSTART-FH study includes patients with FH regardless of the concomitant LDL-lowering therapies and the presence of coronary artery disease. In this study, the primary endpoint is the absolute change of LDL cholesterol. The secondary endpoints are as follows: the absolute change/the per cent change of fasting glucose at 12 months from baseline, cost during the study period, the absolute change/the per cent change of blood pressure at 12 months from baseline, the absolute change/the per cent change of serum lipids (total cholesterol, triglycerides and HDL cholesterol) at 12 months from baseline, the absolute change/the per cent change of urine albumin at 12 months from baseline, number of new-onset diabetes, changes in lipid-lowering therapies that occurred during the study period, frequency of use of the smartphone app and the absolute/per cent LDL cholesterol change due to the change of nutritional intake. LDL cholesterol levels can be modulated by dietary intake of fatty acids and cholesterol, and dietary recommendations are the first-line therapy before LDL-lowering therapy. Although some studies have shown that dietary adjustments can reduce plasma cholesterol levels by 10%–30% in patients with FH, a recent meta-analysis has shown that there is no beneficial effects among the patients with FH. In Japan, a conventional in-person nutritional counselling is typically conducted following the diagnosis of FH; then, statin therapy will be introduced. Unfortunately, most of the patients with FH in the real world cannot adhere to an ‘ideal’ diet for a long time, especially through a single conventional nutritional counselling. On this basis, a randomised controlled trial was organised to see if AI-supported automated nutritional counselling using smartphone app is more efficacious than conventional human nutritional counselling in these high-risk patients. We also asked to send pictures of actual dietary intake meals to the patients assigned to conventional nutritional counselling so that reduced dietary intake (of cholesterol) will be understood as actually reducing LDL cholesterol level among those patients. In the conventional arm of this study, the pictures of dietary intake are not reviewed. This is one of the major differences between conventional arm and Asken application arm. In fact, typical conventional dietary counselling in Japan do not collect pictures of dietary intake. On the other hand, the Asken app had been validated in terms of energy and nutrients intakes.

In this study, we do not set any inclusion or exclusion criteria on statin dosages. In fact, there are some FH patients who have been treated using maximum doses of statins with PCSK9 inhibitor, while others not due to a variety of reasons, such as statin intolerance, patients’ preference and medical costs. We wanted to clarify if we can reduce their LDL cholesterol via dietary counselling using smartphone app.

This study has several strengths and limitations. This would be the first randomised controlled trial in the world to assess the efficacy of AI-supported nutritional counselling among patients with FH. This study is conducted in a single-centre manner; it is not a double-blind study. We will not
record their physical activity in this study, which may affect the results. Young female patients who are expecting to get pregnant would be excluded, which may lead to some bias. All the study participants need to use this app. This may be a barrier, especially to the elderly people who have some difficulty to use smartphone. This app was validated in Japanese women (a population that may have significantly lower enrolment in this particular study) and may not be completely reliable in other populations.

In conclusion, this study aimed to demonstrate the study design and protocol of the iSTART-FH study. AI-supported automated nutritional counselling is hypothesised to reduce LDL cholesterol to a larger degree than that of conventional human nutritional counselling in patients with FH. The fact that dietary intake of cholesterol is actually affecting serum level of LDL cholesterol in these patients will also be demonstrated. Finally, this study will provide insights into the importance of continuous nutritional counselling to patients with FH.

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