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Effects of artificial intelligence-SsupporTed 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 and mobile-supported nutritional intervention using this technique may be an alternative approach to traditional nutritional counselling in person. This study aims to test the hypothesis that AI-supported nutritional 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); all recruited patients are required to provide written informed consent. 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.

Trial registration number UMIN000040198.

INTRODUCTION

Familial hypercholesterolaemia (FH) is an autosomal dominant genetic disorder, and the prevalence of patients with heterozygous FH in the general population is approximately 0.2%–0.5% (1 in 200–500 individuals).[1–5] FH is characterised by hyper low-density lipoprotein (LDL)-cholesterolaemia and systemic xanthomas from infancy, and it is one of the leading causes of premature coronary artery disease.[6] Treatment for FH is a lifelong process, as it is the total lifelong exposure to LDL cholesterol that eventually leads to the development of coronary artery disease.[4] Both medical treatments and dietary counselling are recommended, and the treatment target of LDL cholesterol among patients with FH is set to $100\,mg/dL$ for primary prevention and $70\,mg/dL$ for secondary prevention in Japan.[1] Although a variety of lipid-lowering therapies, including

statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors, already exist,[7] nutritional counselling is still fundamental in the approach to this common genetic disorder. Currently, a nutritional counselling is recommended in this disorder. However, it is difficult to perform such counselling in-person due to lack of healthcare resources.[8] Moreover, it remains uncertain about the beneficial effect by traditional dietary intervention for the patients with FH.[9] Technological advancement, including remote healthcare devices, may lead to a higher impact in dietary self-monitoring.[10 11] In addition, dietary self-monitoring has led to the behavioural changes,[12] and it is quite interesting to note that use of electronic record led to better adherence to their dietary self-monitoring.[13] Furthermore, artificial intelligence (AI) has enabled us to identify food items automatically, and it provides real-time feedback on a patients' nutritional intake.[14] These apps will be useful tools for patients with FH in terms of their dietary counselling. Accordingly, this study aims to demonstrate the efficacy of automated nutritional intervention using smartphone app supported by AI on reducing LDL cholesterol, compared with conventional nutritional counselling in-person in patients with FH.

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
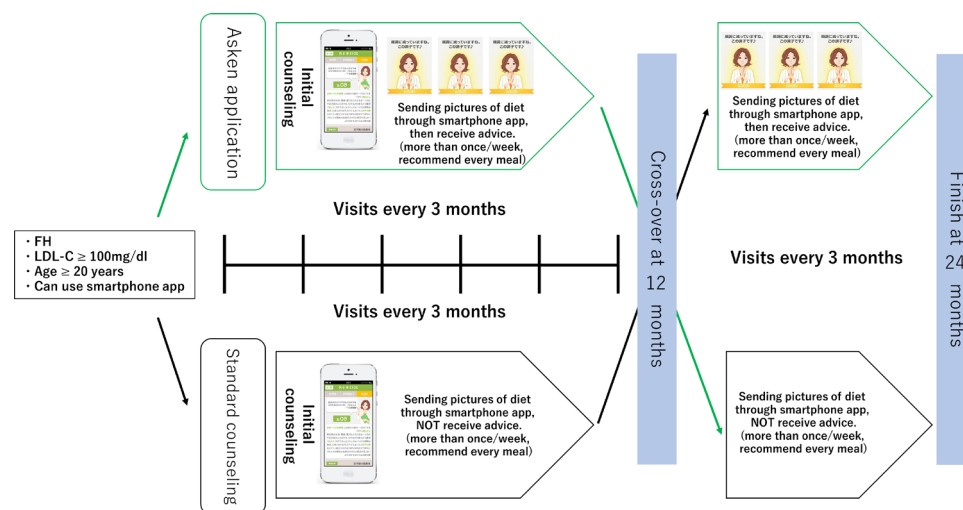

Figure 1 Study flow. Patients with FH aged 20 years or over who can use the smartphone app will be randomly divided into two groups (Asken application group or standard counselling group). Asken application group: after the initial counselling, the use of the smartphone app is started. They are asked to send pictures of their diet through the app (more than once a week, recommended as every meal), and the app will send them advice based on their intake. follow-up at the outpatient clinic is once every 3 months. After 12 months, they are assigned to standard counselling group, and they will not receive advice from the APP, although they are asked to keep sending pictures of every meal. Standard counselling group: after the initial counselling, the use of the smartphone app is started. They are asked to send pictures of their diet through the app (more than once a week, recommended as every meal), but the app will not send them advice. Follow-up at the outpatient clinic is once every 3 months. After 12 months, they are assigned to the Asken application group, and they will receive advice from the app based on their intake. FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol.

Table 1 Assessment and evaluation schedule of this study

Variables		Preobservation period	Intervention period				Cross-over	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	→						

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 behavioural 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

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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).
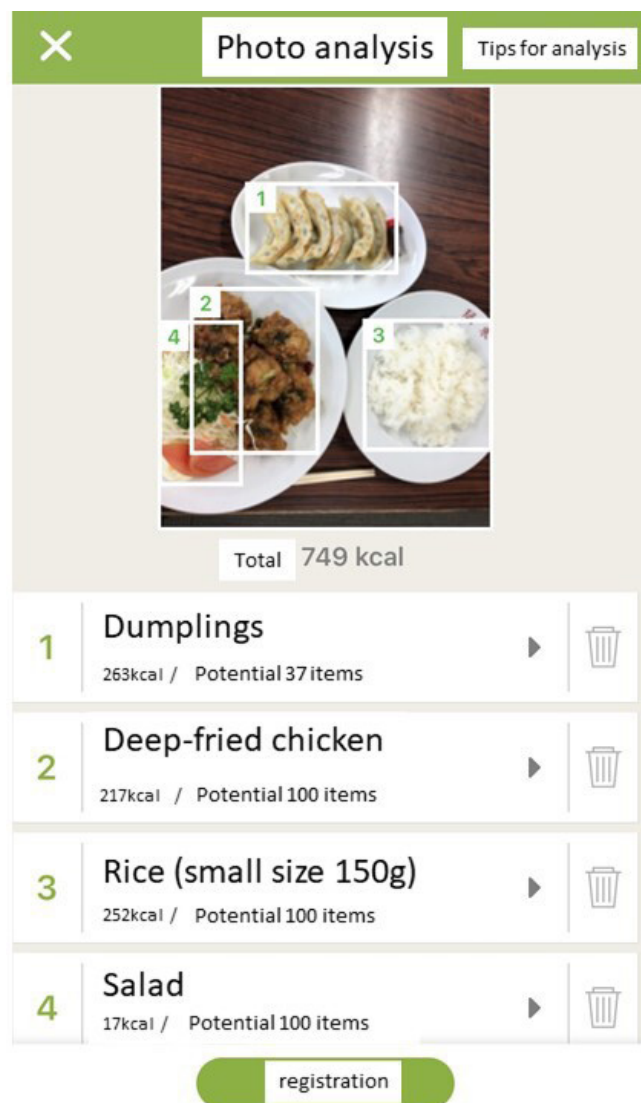9. Under treatment of malignancies.

Figure 2 Artificial intelligence (AI)-powered photo analysis of a meal. Deep learning AI analyses the photo of the entire meal and identifies the frame of each item as well as its menu and serving amount.

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
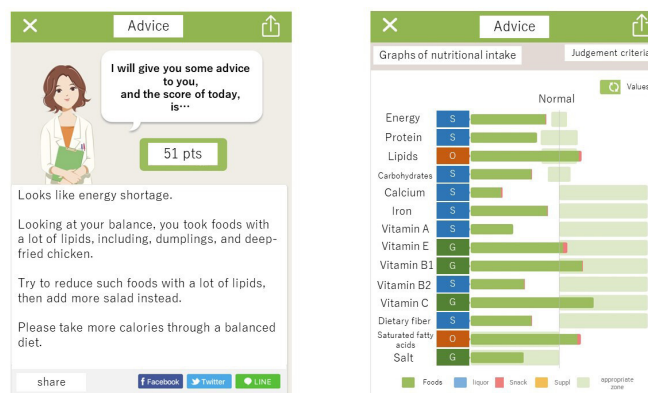

Figure 3 Advice from the smartphone app. Left. A score and feedbacks. A score, and feedbacks are provided by a Japanese character named 'Miki'. Right. A chart of energy and nutrient intakes. Intakes of energy, protein, lipids, carbohydrates, calcium, iron, vitamin A, vitamin E, vitamins B_1 and B_2, vitamin C, dietary fibre, saturated fatty acids and salt are displayed.

MiSeq system. The variant is defined as causal when it fulfils 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,[17 18] 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 $\alpha=0.05$, 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,[17 18] 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.[16]

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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