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eHelp China: A Randomized Trial Evaluating the Benefits of a Smartphone-Based Patient Support Tool

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Abstract

Background: Statins reduce low-density lipoprotein cholesterol (LDL-C) and thereby cardiovascular Received: January 15, 2021 risk, but treatment adherence is often suboptimal. Mobile health (mHealth) technology may facilitate Accepted: June 26, 2021 adherence in a cost-effective manner. This study evaluated whether a smartphone-based patient support Published: June 28, 2021 tool could improve adherence and prolong statin treatment duration.

Methods: This randomized, two-arm, 24-week, phase IV study (NCT02433288), conducted at 26 Keywords: cardiology departments across hospitals in China between July 2015 and October 2016, included adult patients (18-80 years) with dyslipidemia/hyperlipidemia at high cardiovascular (CV) risk who were newly eHealth/telemedicine/mobile prescribed rosuvastatin. Eligible patients received either a smartphone-based patient support tool (active health, Health care delivery, group) or a control app (control group). Both groups completed an adherence questionnaire via their Treatment adherence smartphone.

Results: Primary outcome was the duration of statin treatment; secondary outcomes were the percentage of fully adherent patients, rate of treatment adherence, and percentage change in LDL-C at week 24. Treatment duration was longer in the active group vs the control group (mean 157 days vs 146 days; P= 0.0019). However, fewer patients in the active group than in the control group rated themselves as fully adherent (4.4% vs 9.9%; P= 0.0017), and the overall reported treatment adherence was lower. At week 24, there was no difference in LDL-C reduction between the groups.

Conclusion: The use of mHealth addresses suboptimal adherence to statin treatment resulting in a prolonged treatment duration. mHealth has a future in supporting, educating, and motivating patients to be more adherent to drug treatments. More studies are however needed to evaluate similar, affordable support tools and technologies.

Introduction

Cardiovascular (CV) disease (CVD) is the leading cause of death globally, with an estimated 17.7 million deaths annually [1]. Risk factors for CVD, including hypercholesterolemia, can be controlled through behavioral changes and appropriate treatment [2]. Statins are a well-established option in dyslipidemia management and can reduce both primary and secondary CV risks [3-5]. A large metaanalysis assessing CV risk reduction found that the relative risk of major vascular events reduced by 22% for every 1 mmol/L (39 mg/dL) reduction in low-density lipoprotein cholesterol (LDL-C) by statin therapy, a benefit that was maintained throughout treatment [3].

Current international guidelines recommend statin therapy for patients with raised LDL-C levels [4,5]. However, two-thirds of very high-risk patients globally do not reach their LDL-C target [6]. Approximately 200 million adults in China have LDL-C levels \geq 3.4 mmol/L (\geq 130 mg/dL) [7]. These data suggest lack of awareness, among patients and physicians, of dyslipidemia and its consequences, and poor disease management.

Publication History:

Numerous studies demonstrate that multiple, face-to-face cognitive education and counseling sessions improve treatment adherence and outcomes [8]. Unfortunately, these techniques are often resource intensive, involving time and costs. Mobile health (mHealth) technology, e.g., smartphone- or tablet-based applications, could provide an alternative intervention to improve treatment duration and adherence among patients in a cost-effective manner. This study investigated the impact of a smartphone-based patient support tool on the duration of rosuvastatin treatment in China.

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Materials & Methods

Study design

The eHelp China study (NCT02433288) was a randomized, twoarm, 24-week, phase IV study (Figure 1). The protocol was approved by an institutional ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki 1975, and revised as per the 41st World Medical Association General Assembly, Hong Kong, 1989. The study was conducted at 26 cardiology departments across hospitals in China between July 2015 and October 2016 and included adult patients (18-80 years) with dyslipidemia or hyperlipidemia at high CV risk who were newly prescribed rosuvastatin (inclusion and exclusion criteria are listed in Table S1 from the Supplementary file).

Patient and public involvement

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

Randomization and data collection

Randomization was performed using sequentially numbered sealed envelopes. Eligible patients were randomized (1:1) to receive a smartphone-based patient support tool (active group) or a smartphone-based control application (control group). In the active group, the smartphone application contained the patient support tool and questions for recording patient-reported outcomes (PROs). Patients in the active group received feedback on their rosuvastatin treatment and disease support and information, treatment, and lifestyle choices. In the control group, patients had no access to the smartphone-based patient support tool, but the smartphone application was used to collect PROs. The smartphone application was provided in addition to the normal standard care. No drug was distributed via the study; patients purchased their rosuvastatin prescription as in normal practice.

Study procedures

Written informed consent, patient demographics, medical and smoking history, and clinical assessments were obtained at visit 1 (baseline); clinical assessments, also conducted at the end of the study (visit 2), included physical examination, height, body weight, body mass index, systolic and diastolic blood pressure (BP), and lipid profile (LDL-C, total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], and triglyceride [TG] concentrations). For patients receiving ≤ 7 days of treatment since starting rosuvastatin, the lipid level before statin treatment was used as the baseline value. No clinical assessment was used for directing the treatment of patients. As the study evaluated the smartphone-based patient support tool, and rosuvastatin was not considered an investigational product for the study, adverse events, except for serious adverse events, were not reported.

Both groups used the application to record treatment adherence using the Rosuvastatin Adherence Questionnaire (RAQ) every 4 weeks±3 days, attitudes and beliefs about medication using the Beliefs about Medicine Questionnaire-General (BMQ-G) [9], and current lifestyle habits using the Lifestyle Questionnaire (LSQ) at visits 1 (LSQ-V1) and 2 (LSQ-V2).

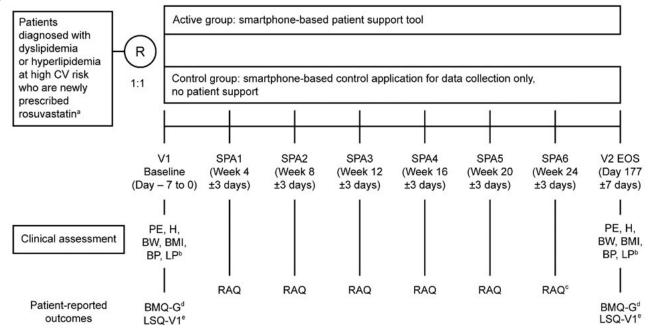


Figure 1: Study design.

^aStatin naïve or no statin use during the last 4 weeks prior to enrollment, except for patients receiving ≤ 7 doses of statin during current hospitalization before enrollment; ^bLipid levels at admission before statin treatment to be used for patients receiving ≤ 7 doses of statin during current hospitalization; ^cAvailable for completion by the patient until the end of visit 2; ^dBMQ-G prompted via smartphone on the day of visit 1 and after week 24; ^cLSQ prompted via smartphone on the day of visit 1 (LSQ-V1) and after week 24 (LSQ-V2).

Abbreviations: BMI: body mass index; BMQ-G: Beliefs about Medicine Questionnaire-General; BP: blood pressure; BW: body weight; CV: cardiovascular; EOS: end of study; H: height; LP: lipid profile; LSQ: Lifestyle Questionnaire; LSQ-V: Lifestyle Questionnaire at Visit; PE: physical examination; R: randomization; RAQ: Rosuvastatin Adherence Questionnaire; SPA: smartphone assessment; V: visit.

During clinic visit 1, patients were prompted with the BMQ-G and LSQ-V1. The smartphone application was activated after responses to the questions had been recorded. Patients in the active group were instructed on the use of the smartphone-based support tool before leaving the hospital. Patients were prompted to complete the RAQ on their smartphone every 4 weeks. After week 24, the smartphone application prompted patients to complete the BMQ-G and LSQ-V2 and return to hospital for visit 2.

Twenty patients in the active group participated in a 60-minute one-off semi-structured telephone interview on the support tool. Patients were asked open-ended questions to elicit in-depth feedback and closed questions for quantitative rating of how helpful, easy to understand, and relevant they found certain aspects of the support tool rated on a scale of 1 to 5 (1 indicating a negative response; 5, a very positive response).

Patients continued visiting their physician for clinical assessments throughout the study, but these visits did not form part of the study nor were they used to instruct treatment decisions.

Smartphone-based patient support tool

The patient support tool software was installed on the smartphones of patients in the active group. The application aimed to increase the rosuvastatin treatment duration (medication and lifestyle practices) by addressing the main modifiable behavioral reasons for non-adherence through a combination of methods [9]. These methods included: providing information regarding the necessity of treatment and the importance of medication; disease motivational and supportive messages, treatment, and lifestyle advice; visuals on how lifestyle choices affect CV risk; reminders for medicine intake and prescription refill; and sharing of patients' data with nominated caregivers. For example, the tool contained screens providing medical knowledge; patient education with daily and weekly messages; an e-diary of adherence, lipid levels, blood pressure, exercise, and body weight; individual goal setting for body weight and exercise; a treatment index to visualize overall progress; and game elements with a personalized Avatar and surprise rewards to extend interest from patients. Figure S1 shows sample screenshots from the smartphonebased support tool. After installing and initiating the smartphone application, patients entered their baseline information. Thereafter, the support tool allowed patients to enter data on an ongoing basis and provided feedback, based on the information provided.

Patient-reported outcome tools

The RAQ included 12 questions to capture adherence to rosuvastatin (Table S2, Supplementary file), which included questions on prescription, adherence, and patients' assessment of outcomes. The BMQ-G tool comprised two 4-item factors assessing beliefs that medicines are harmful, addictive, poisonous, and should not be taken continuously ("General-Harm"), and that medicines are overused by doctors ("General-Overuse"), rated on a five-point Likert scale (Table S3, Supplementary file).

The LSQ-V1 and LSQ-V2 questionnaires comprised three questions regarding diet, exercise, and smoking history recorded at enrollment and at the end of the study (Table S4, Supplementary file).

Study outcomes

The study's primary endpoint was the duration of rosuvastatin adherence (time from randomization to the last patient-reported visit Int J Clin Res Trials ISSN: 2456-8007 to a doctor for prescription renewal plus the number of days since the last prescription). Secondary endpoints evaluated the effect of the smartphone-based patient support tool vs standard patient support on the percentage of fully adherent patients (defined as the number of patients who answered "Yes" to the question "Over the past 4 weeks, did you take your rosuvastatin pills every day?" at all time points divided by the total number of randomized patients); treatment adherence (assessed on patient-reported number of rosuvastatin tablets taken divided by the total number of days in the study); and percentage change in LDL-C from baseline to week 24.

Statistical analysis

For power calculation, assuming a median time to the last day of rosuvastatin treatment of 82 days for the control group, 388 completers per group would provide 80% power (two-sided P= 0.05) to detect a median difference in the time to the last day of rosuvastatin treatment of 22 days. A "completer" was a patient with evaluable information for the primary endpoint. Assuming a dropout rate of 10%, 862 randomized patients in total were assessed for the primary endpoint.

All analyses of the primary and secondary endpoints were performed per the intention-to-treat principle using the full analysis set (FAS) and included all randomized patients. Survival analysis assessed rosuvastatin adherence by using a log-rank test of the time to the last day of rosuvastatin treatment (defined as the last patientreported visit to a doctor for rosuvastatin prescription renewal plus the number of days of the last prescription); P<0.05 was considered statistically significant. For secondary objectives, the percentage of fully adherent patients was compared between the groups using a Chisquare test; the mean difference between patient-reported treatment adherence rate for each group was analyzed using an independent samples z-test for proportions; percentage change in LDL-C from baseline at week 24 was analyzed using a linear model with group (active/control) as fixed factor and baseline LDL-C as covariate, and was presented as the difference in mean percentage change and 95% confidence interval (CI).

Continuous data were presented as mean±standard deviation (SD) or median (range); categorical data were presented as an absolute number (proportion).

Results

Demographic and baseline characteristics

In total, 13,540 patients were screened; 6,688 patients did not have elevated lipids, 3,606 were statin naïve or unsuitable for the study, 1,656 did not have a suitable smartphone, and 736 declined participation. Therefore, 854 patients were included in the FAS, 431 were randomized to the active group, and 423 to the control group.

In the overall population, 63.1% were women and mean±SD age was 54.6 ± 9.7 years (Table 1). The two groups were well matched and representative of patients with dyslipidemia in China who may be prescribed rosuvastatin. On average, patients used the smartphone-based patient support tool frequently for the first 7 weeks, with duration of use ranging from 2 days to 24 weeks.

Primary outcome

During the planned 169-day window (time from randomization to planned last date of the last RAQ), 15.6% of patients in the active

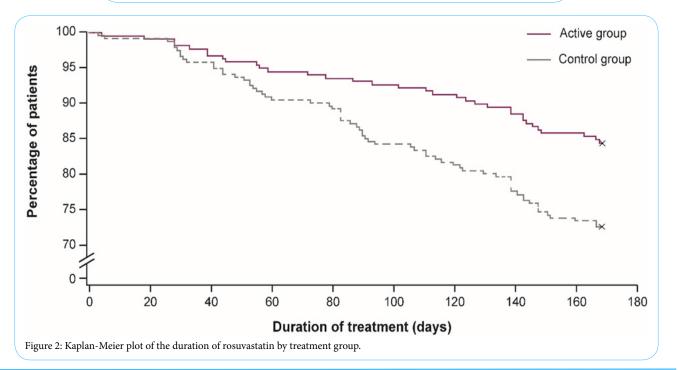
group and 27.5% of patients in the control group stopped rosuvastatin treatment (Figure 2). The mean duration of rosuvastatin treatment (time from start of the study to last response of "yes" to the RAQ question "Over the past 4 weeks, did you see a doctor to get your rosuvastatin prescription?" plus duration of prescription, typically 14-28 days) was 157 days in the active group and 146 days in the control group; log-rank test was conducted for determining equality between the active and control groups (P= 0.0019).

Two post-study sensitivity analyses further investigated the impact of the patient support tool on rosuvastatin treatment. In the first analysis, treatment duration was limited to the time the patient first answered "no" to the RAQ question. The mean duration of rosuvastatin treatment was 105 and 99 days, respectively, for the active and control groups (log-rank test for equality between active and control groups, P= 0.0972) (Figure 3A). In the second sensitivity analysis, the 169-day time frame limitation was removed with mean

	Active group (n=431)	Control group (n=423)	Total (n=854)	
Age, years	54.7±9.8	54.5±9.5	54.6±9.7	
Sex				
Female, n (%)	270 (62.6)	269 (63.6)	539 (63.1)	
BMI, kg/m ²	25.6±3.3	25.9±3.2	25.7±3.3	
BP, mmHg				
Systolic	132.1±17.1	131.6±17.9	131.9±17.5	
Diastolic	80.1±11.4	80.2±11.8	80.1±11.6	
Lipid levels, mmol/L				
LDL-C	3.59±0.72	3.59±0.65	3.59±0.69	
TC	5.46±0.99	5.43±0.87	5.45±0.93	
HDL-C	1.18±0.35	1.18±0.31	1.18±0.33	
TG, median (range)	1.59 (0.31, 4.51)	1.63 (0.49, 4.50)	1.62 (0.31, 4.51)	
Current smokers, n (%)	126 (29.6)	129 (31.0)	255 (29.9)	
Angina pectoris, n (%)	180 (41.5)	169 (40.2)	349 (40.9)	
Arteriosclerosis, n (%)	45 (10.4)	56 (13.3)	101 (11.8)	
Myocardial infarction, n (%)	39 (9.0)	42 (10.0)	81 (9.5)	
Cerebral infarction, n (%)	14 (3.2)	18 (4.3)	32 (3.7)	
Cardiac failure, n (%)	6 (1.4)	4 (1.0)	10 (1.2)	
Hypertension, n (%)	294 (67.7)	269 (64.0)	563 (65.9)	
Diabetes, n (%)	99 (22.8)	87 (20.7)	186 (21.8)	

Table 1: Demographic and baseline characteristics in the full analysis set population. Data are mean±SD, unless otherwise stated.

Abbreviations: BMI: body mass index; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SD: standard deviation; TC: total cholesterol; TG: triglycerides.



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treatment duration of 134 days and 128 days in the active and control groups, respectively (log-rank test for equality between active and control groups, P= 0.0891) (Figure 3B).

Secondary outcomes

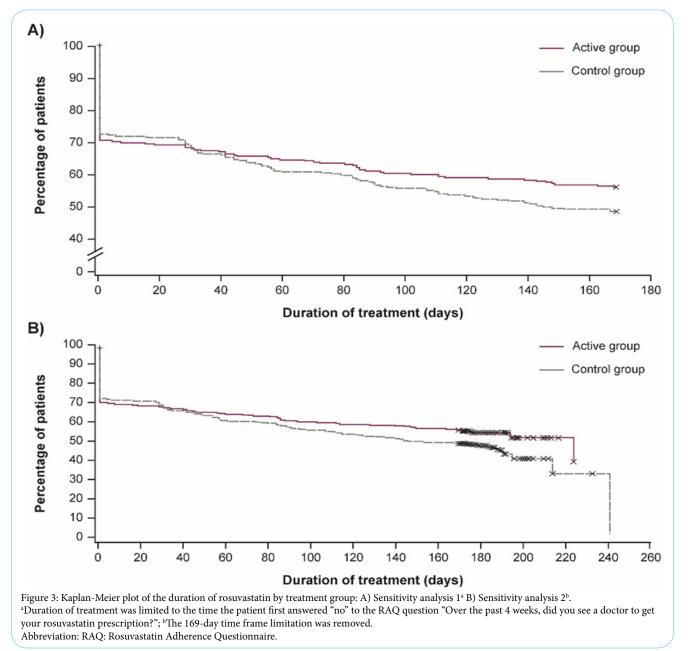
A significantly smaller percentage of patients in the active group were fully adherent compared with the control group (19/431 [4.4%] vs 42/423 [9.9%]; P= 0.0017). The number of patients completing all RAQs was 28 and 62 in the active and control groups, respectively. The mean±SD overall adherence (reported number of pills taken divided by number of days in the study) was 38%±33% and 58%±36% in the active and control groups, respectively.

The percentage change in LDL-C from baseline to week 24 was the same for both groups (0.63% [95% CI: -3.27%, 4.53%]). A comparison of the change from baseline to week 24 showed no statistically

significant difference between the groups. Changes from baseline to week 24 for TC, HDL-C, and TG were similar between the two groups (Table 2).

Patient responses to RAQ, BMQ-G, and LSQ

Answers to questions 6 to 12 of the RAQ were alike between the two groups at weeks 4 to 24. Sum scores between baseline and postbaseline in both "overuse" and "harm" scales were similar for BMQ-G. For "overuse," the mean score was 10.7 and 11.2 in the active group and 10.8 and 11.0 in the control group at baseline and at week 24, respectively. For "harm," the mean score was 10.5 and 10.8 in the active group and 10.8 and 11.0 in the control group at baseline and at week 24, respectively. Responses to the lifestyle questionnaire were also similar between the two groups. Approximately half of the patients reported that they ate a healthy diet at baseline, but when asked at the end of the study, this figure rose to 76%-79%. Similarly, 43%-46% of



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patients reported that they exercised regularly at baseline, with this figure rising to 76%-77% at study end. There was a small drop in the number of people who reported that they smoked between the start and the end of the study (17%-18% at baseline vs 10% at end of study).

Interview

Thirteen patients in the active group participated in the 60-minute one-off telephone interview; 11 were conducted in full but two patients finished early due to time constraints. The mean age of the interviewees was 56.3 years and 62% were men. Overall, patients found the support tool easy to navigate, rating it a median of 4 on a scale of 1 to 5 (1 indicating a negative response and 5 a positive response), and the information provided by the support tool helpful (median score 4), easy to understand (median score 5), and relevant (median score 5). Patients also found the messages and images clear to read and the touchscreen easy to use. Furthermore, 42% reported that the reminders function was the best aspect of the support tool. A quarter said that they liked the daily medical knowledge notifications best, e.g., tips on diet and exercise.

Figure 4 shows the investigators' assessment of various aspects of the support tool.

Discussion

The eHelp China study evaluated the effects of an innovative, smartphone-based patient support tool on treatment duration and

adherence in patients newly prescribed rosuvastatin in China. The primary outcome of mean duration of treatment was 157 days in the active vs 146 days in the control group, which was a statistically significant difference (P= 0.0019).

The active cohort of both groups lacked behavioral consistency over time; many patients displayed a multievent behavior with multiple changes (e.g., from reporting having access to rosuvastatin to reporting lack of access and then back again). Therefore, two more conservative analyses were conducted; both analyses showed a trend towards prolonged duration of treatment with the active application, but the difference was not statistically significant, probably because of the substantial censoring in the active and control groups.

The study also investigated full adherence to treatment and found that, in contrast to treatment duration, more patients in the control (9.9%) than in the active group (4.4%) reported taking their tablet every day (P< 0.05). However, when only those patients who completed all RAQs were analyzed, the percentage of fully adherent patients was the same in each group (67.9% in the active and 67.7% in the control group; P= 0.99).

The overall adherence data were likely impacted by the difference in RAQ response frequency between the two groups. Fewer patients in the active group than in the control group completed their monthly RAQs (n=200 vs n=219, respectively). If all missing data were set to 0% adherence, the reported results were 38.0% and 58.2% in the

Lipid (mmol/L)	Active group (n)	Control group (n)	Change from baseline for active group vs control group (mmol/L)	95% CI	P value
LDL-C	303	303	0.63	-3.27, 4.53	0.7514
TC	303	303	-0.21	-3.59, 3.16	0.9011
HDL-C	301	302	-1.57	-5.01, 1.87	0.3700
TG	303	303	9.36	-0.21, 18.93	0.0553

Table 2: Changes in lipids from baseline to week 24.

Abbreviations: CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

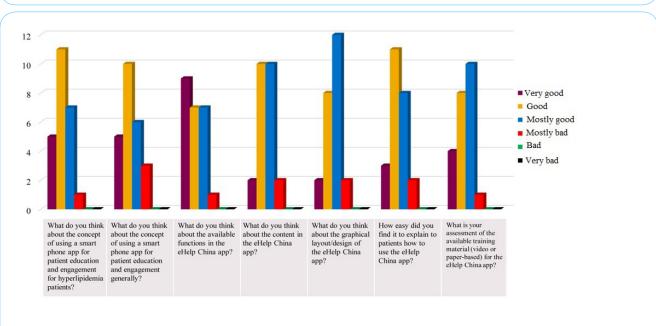


Figure 4: Investigators' assessment of the smartphone-based support tool.

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active and control groups, respectively. However, if only data actually reported were used, i.e., no value imputed for missing data, the corresponding values were 94.6% and 96.0%, respectively (P=0.39).

Funding

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Role of the Funder/Sponsor

Patients in the active group also had access to an online diary via the support tool and may have more accurately recorded their tablet intake compared with patients in the control group, who had to rely on memory.

Similar studies investigating the impact of mHealth on statin treatment duration have found significant differences in adherence when mHealth technology is used [10,11]. In a study investigating the impact of an interactive voice response technology on behavior change, patients receiving tailored feedback were significantly more likely to take statins at a particular time point compared with patients receiving generic feedback [10]. In another study, patients using a support tool that compiled dosing history (patients used the device to record when a tablet was taken) and educational reminders significantly increased statin adherence compared with patients not using the tool [11].

A small number of patients from our study also participated in a telephone questionnaire, facilitating a qualitative analysis of the patients' perception about the support tool. Results of the interviews showed that, despite some suggestions for improvement, patients found the support tool easy to navigate, use, and understand and provided helpful and relevant information. As depicted in Figure 4, the investigators were in alignment with the patients. These results are thus consistent with the Technology Acceptance Model, which has been shown to be widely applicable to explaining users' reactions to health information technology in terms of perceived ease of use and usefulness [12].

Conclusions

Patients using the smartphone-based support tool reported a prolonged duration of statin treatment. The authors are confident that mHealth will support, educate, and motivate patients to be more treatment adherent. More studies are needed to further evaluate and develop similar, affordable support tools and technologies.

Competing Interests

Dr Du, Dr Xu, Dr Guo, Dr Li, Dr Mei, Dr Han, Dr Wang, Dr Li, Dr Shen, and Dr Ma have no potential conflicts of interest to declare. Dr Jörntén-Karlsson, Dr Ryden, Dr Ahlqvist, Dr Sundén, and Dr Karlson are current or former employees of AstraZeneca.

Authors' Contributions

All authors were involved in developing the study concept and design, interpreting the data, and developing the manuscript. All authors reviewed and approved the final version of the manuscript for submission.

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AstraZeneca was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. However, ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Ethics Approval

The protocol was approved by an institutional ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki 1975, and revised as per the 41st World Medical Association General Assembly, Hong Kong, 1989.

Patients' Approval

Informed consent was obtained from all study participants prior to any study-specific procedures.

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