RESEARCH ARTICLE

Feasibility of an Integrated Digital and Pharmacological Approach Targeting Blood Lipids in Atherosclerotic Cardiovascular Disease Management

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Abstract

Objectives: Strong evidence supports the importance of lipid-lowering and exercise therapies in the long-term therapy of atherosclerotic cardiovascular disease (ASCVD). Establishing efficient comprehensive intervention programs that combine pharmacological and exercise prescription is crucial to investigate with the aid of digital technologies.

Methods: A convenience sample of 25 ASCVD patients (57.8 ± 9.5 years, 76% males) was gathered. All participants were prescribed with 12-week home exercise program supervised by an app and bimonthly 75mg alirocumab subcutaneous injections. Follow up visits were scheduled at the end of 4th and 12th week.

Results: Nineteen participants completed the program with a retention rate of 76%. Sixteen (84.2%) participants received all six doses of alirocumab. The total management time of the 12-week program added up to 65.47 minutes per patient. Satisfaction score was 4.2 ± 0.6 and the User Version of the Mobile Application Rating Scale (uMARS) overall objective quality score on the app was 3.4 ± 0.7. At the 4-week and 12-week follow-ups, LDL-C levels reduced compared to baseline (-1.5 ± 0.8 mmol/L, $P < 0.001$, -1.6 ± 0.8 mmol/L, $P < 0.001$, respectively), along with TC (-1.8 ± 1.2 mmol/L, $P < 0.001$, -1.6 ± 1.3 mmol/L, $P < 0.001$, respectively), but not TG, HDL-C, GAD-7 and PHQ-9.

Conclusion: The integrated pharmaceutical and digital ERx intervention program was feasible and well accepted in ASCVD patients.

Keywords: cardiac rehabilitation; atherosclerosis; cardiovascular innovation

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CR, cardiac rehabilitation; EET, effective exercise time; ERx, exercise prescription; GAD-7, Seven-item Generalized Anxiety Disorder Scale; HDL-C, high-density lipoprotein cholesterol; IM, instant messaging; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; PHQ-9, Nine-item Patient Health Questionnaire; SD, standard deviation; TC, total cholesterol; TG, triglycerides; uMARS, User version of the Mobile Application Rating Scale.

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a major cause of hospitalization and cardiovascular mortality. Low-density lipoprotein cholesterol (LDL-C) and insufficient physical activity are well-established modifiable risk factors for poor ASCVD prognosis [1]. Thus, blood lipid and physical activity management have been core components of comprehensive cardiac rehabilitation (CR) programs.

Alirocumab was one of the first antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) to be approved by the United States Food and Drug Administration to specifically decrease LDL-C levels and hospitalization events in cardiovascular disease secondary prevention [2]. The role of prescribed exercise in ASCVD secondary prevention is well established [3]. Gaining 1 metabolic equivalent in cardiorespiratory fitness, as is believed to be feasible through an exercise rehabilitation program, would result in a 12%–13% decrease in CVD mortality and all-cause mortality, respectively [4]. Through decreasing PCSK9 expression [5], exercise combined with alirocumab might further benefit patients with ASCVD.

Despite the widely accepted health benefits, barriers including physical distance from treatment centers, a lack of transportation, and time expenditure may prevent eligible candidates from participating in center-based exercise programs. Optimizing the presentation and delivery of the intervention is critical for current CR programs [6]. Recruiting more adequately trained CR providers would aid in improving CR program quality [7], but alternative treatment delivery models with greater consideration of individuals' needs are required to increase adherence and optimize ASCVD outcomes [8].

Advances in digital health applications (apps) have provided new approaches enabling health care professionals to remotely deliver, monitor, or track exercise programs tailored to the needs of patients in home or community environments [8]. Despite their rapid growth in number, mobile health apps focusing on delivering home-based exercise programs are relatively rare. The Xuezhijing app (developed by RECOVERY PLUS, Inc.) is a commercial full video guided remote exercise prescription (ERx) app, which was designed to provide medical professionals with a novel digital approach to prescribe individually tailored home-based exercise treatment for patients with ASCVD with multiple CVD risk factors. The app includes health fitness testing, aerobic based multicomponent exercise, exercise tracking, heart rate monitoring, and video guided courses.

We believe that combining home-based digital ERx and alirocumab in an integrated novel ASCVD intervention program could improve patient-caregiver interaction, increase CR enrollment, and optimize health outcomes, in a patient-centered manner.

Objective

The aim of this study was to evaluate the feasibility of an integrated intervention program featuring alirocumab combined with home-based digital ERx, powered by the Xuezhijing app, in patients with ASCVD.

Methods

Study Design

The present study was a prospective single-arm feasibility study. Eligible participants were older than 18 years; had diagnosed ASCVD (stable angina, history of acute coronary syndrome, or post-coronary revascularization), had been prescribed or were taking no more than 2 doses of alirocumab, with or without statin, and were capable of operating a smartphone.

The exclusion criteria were the presence of any conditions that might potentially affect or be aggravated by exercise, including unstable cardiovascular health condition, acute systematic disease, or absolute or relative contraindications for exercise training, according to current cardiac rehabilitation guidelines [9].

Participants volunteered to be recruited through a convenience sampling method in the cardiology ambulatory care setting at the First Affiliated Hospital of Ji'nan University. The study protocol weas reviewed and approved by the Research Ethics Review Committee of the First Affiliated Hospital of Jinan University (KY-2021-085) and was registered with the National Medical Research

Registration Information System (ID: MR-44-22-008454). All participants provided signed informed consent before recruitment into the study.

Integrated Intervention

All participants had identical alirocumab schedules and were prescribed 75 mg alirocumab delivered through biweekly subcutaneous injections performed the by either the patients themselves or their caregivers.

All participants were prescribed a 12-week home-based exercise program and biweekly subcutaneous injections of alirocumab by a single qualified clinician. Other ASCVD therapies followed the clinical guidelines. After recruitment, the descriptive information collected at baseline included sex, age, diagnosis, treatment, educational level, exercise habits, and blood lipid profile. After baseline fitness assessments, participants received a brief training in using the Xuezhijing app. They were then provided with instructions for their alirocumab schedule, and an in-app medication reminder was set up.

Two versions of the Xuezhijing app were used: a professional client for clinicians and a user client for patients. The patient-end app was accessed via tablet. Moderate intensity aerobic-based exercise was prescribed (Figure 1A) for each participant with an individually determined target heart rate at 40%–60% of the heart rate reserve. The app automatically logged the effective exercise time (EET), defined as the exercise duration within the prescribed intensity (Figure 1B). Weekly exercise goals were set to 150–250 minutes EET progressively within 1 month, with 20–50 minutes EET recommended per session. A multicomponent exercise video playlist presented in the app was formulated from a battery of >3000 exercises. The playlist included videos automatically narrated by the app, and training stages presented consecutively in the following order: warm up, cardiovascular exercise mix (main training phase), and cool down.
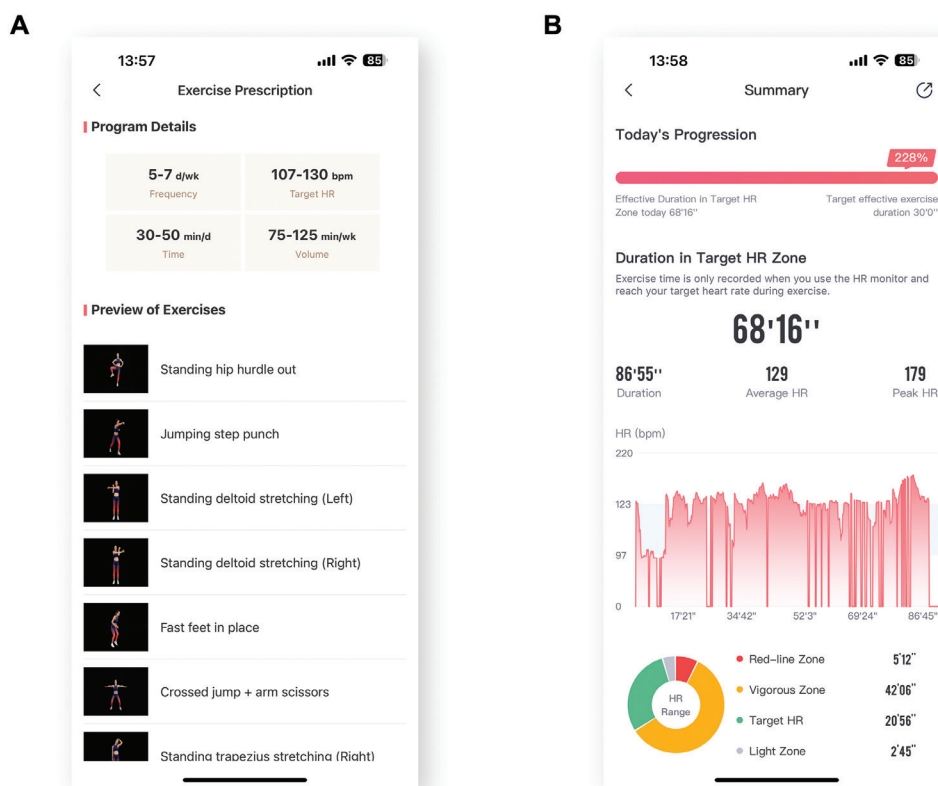
Figure 1 Screenshots of the Xuezhijing App.
(A) The ERx, containing the exercise frequency, target heart rate, session time, weekly exercise volume, and preview of exercise movements. (B) The exercise session summary, containing today's progression, duration in target heart rate zone or effective exercise time, graphical heart rate record, exercise intensity distribution ring, and other detailed information.

The physician was able to evaluate the objective data indices and subjective feedback provided by participants following the. Notable information appeared in the "to be processed list" section in the physician's client, including subjective reports of discomfort, heart rate spikes exceeding predetermined limits during exercise, and excessively high or low perceived exhaustion degree. The investigator reviewed the "to be processed list" (in-app checklist containing deviations in perceived exertion scores and symptom feedback) daily and the exercise executive summary weekly. Adjustments were made to keep participants exercising within the proper intensity and volume.

Interaction and Follow-Up

The clinician contacted the participants on schedule to increase adherence. Two formatted messages containing reminders and encouragement were sent every week through an instant messaging (IM) app. One-on-one consultations were provided, either through the IM app or by telephone, depending on the complexity of the content.

All participants were requested to attend two outpatient visits during the study at the end of weeks 4 and 12. During the follow up visits, participants underwent blood lipid testing, and completed the Nine-item Patient Health Questionnaire (PHQ-9) [10] and Seven-item Generalized Anxiety Disorder Scale (GAD-7) [11]. Additionally, the in-app user version of the Mobile Application Rating Scale (uMARS) [12] and a 5-point Likert satisfaction questionnaire were completed at the second follow-up. Furthermore, the clinician provided information support as necessary.

Primary Outcome Measures

Feasibility of the Integrated Intervention Program

Feasibility was assessed according to the retention rate, time commitment, adherence, and acceptability of the program. Participants who completed the 12-week follow up were considered to have completed the program. The retention rate was defined as the ratio of participants who completed the program. Time commitments were estimated by the investigator. Adherence was defined as the ratio of ERx completion. The ERx was set on a weekly basis; therefore, the ERx completion rate was calculated according to the number of ERx goal completion weeks. Acceptability was assessed with a participant satisfaction questionnaire according to a 5-point Likert scale (1 = very dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, and 5 = very satisfied). A satisfaction score above 3/5 was considered acceptable.

Secondary Outcome Measures

Usability of the Xuezhijing App

Usability was assessed with the uMARS score. A uMARS score ≥3 was considered acceptable.

Blood Lipid Profiles and Mental Health

Participants' blood lipid profiles and mental health information after 4 weeks and 12 weeks of the intervention were collected and analyzed. Blood lipid profile tests included LDL-C, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). Mental health was evaluated with the GAD-7 and PHQ-9 scales, representing levels of anxiety and depression, respectively.

Statistical Analysis

Because this was a single-arm feasibility study, sample size calculation was not applicable. A convenience sample of patients with ASCVD was recruited.
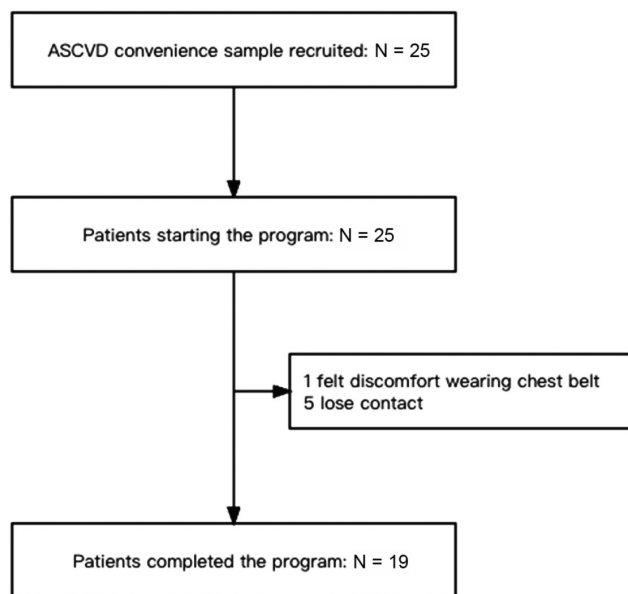
All statistical analyses were conducted in SPSS Statistics for Windows, version 26 (SPSS Inc). We performed Shapiro-Wilk tests to determine whether the differences in data were normally distributed, and then used paired T-tests (two-sided) to assess before-after changes in normally distributed data. To analyze non-normally distributed data, we employed nonparametric statistical tests to examine potential significant differences between the groups. For paired samples, we utilized the Wilcoxon signed-rank test, while for three or more independent samples, we employed the Kruskal-Wallis test.

All data are presented as mean ± standard deviation. The potential clinical meaningfulness was evaluated according to statistical significance with a threshold of $P < 0.05$.

Results

Baseline Characteristics

A total of 25 eligible patients with ASCVD consented to participate in the study, and 19 participants completed the program (Figure 2). One participant dropped out after exercising eight times for a total of 101.7 minutes, because of "feeling uncomfortable when wearing the heart rate chest belt." For five participants, contact was lost in early stages without a reason provided in the feedback. Despite several attempts, the patients could not be reached.

The patient characteristics are shown in Table 1. The mean age of the 25 participants was 57.8 ± 9.5 years (range 29–75 years), and 19 of 25 (76%) were men.

Figure 2 Study Flowchart.

Feasibility of the Integrated Program

Retention Rate and Adherence

Nineteen participants completed the integrated intervention program and filled out all scales and questionnaires as requested. The retention rate was 76%.

Of the 19 participants who completed the program, 1336 exercise sessions were performed during the 12-week period. The total exercise duration was 48128.1 minutes, whereas the total EET was 34844.7 minutes; therefore, 72.4% of participants' exercise was within the prescribed intensity. For each participant, the total EET was 1833.9 ± 1032.7 minutes, and the EET per session was 25.2 ± 6.8 minutes. The weekly EET was 152.8 ± 86.1 minutes per person.

Sixteen (84.2%) participants received all six doses of alirocumab, whereas three received only the initial dose.

Table 1 Baseline Characteristics of Participants in the Study.

Baseline characteristics	Participants, n = 25 mean (SD) or frequency (%)	Completers, n = 19 mean (SD) or frequency (%)	Dropouts, n = 6 mean (SD) or frequency (%)
Age, years	57.8 (9.5)	56.6 (10.6)	61.7 (2.5)
Male (%)	19 (76%)	15 (78.9%)	4 (66.7)
Level of education, n (%)			
Below high school	12 (48%)	8 (42.1%)	4 (66.7%)
High school	9 (36%)	7 (36.8%)	2 (33.3%)
Tertiary level or higher	4 (16%)	4 (21.1%)	0
BMI	24.4 (2.6)	24.1 (2.8)	25.1 (1.8)
RHR	73.2 (10.1)	72.1 (10.9)	76.5 (6.3)
mMRC	0.08 (0.28)	0.1 (0.3)	0
Comorbidities, n (%)			
Dyslipidemia	17 (68%)	14 (73.7%)	3 (50%)
Primary hypertension	18 (72%)	13 (68.4%)	5 (83.3%)
Type 2 diabetes	7 (28%)	5 (26.3%)	2 (33.3%)
Hyperuricemia/gout	9 (36%)	7 (36.8%)	2 (33.3%)

BMI: body mass index; RHR: resting heart rate; mMRC: modified Medical Research Council dyspnea scale.

Time Commitment

Time commitment was estimated after completion of all interventions. The initial instruction regarding the alirocumab treatment plan, app use, and fitness test required approximately 30 minutes per patient. For each participant during the 12-week period, we sent 24 formatted messages through the IM app, sent 3.84 ± 1.57 one-on-one IM inquiries, and conducted 0.68 ± 1.25 one-on-one phone consultations. The estimated time expenditure was 6 minutes, 19.2 minutes, and 10.3 minutes, respectively. Additionally, checking exercise logs and adjusting ERx required approximately 5 minutes per person every week. The total management time for the 12-week home-based exercise intervention program was 65.47 minutes per patient, excluding outpatient visit time.

Acceptability

All 19 (100%) participants who completed the program provided ratings on a 5-point satisfaction Likert scale. The mean satisfaction score was 4.2 ± 0.6, indicating good acceptability of the program.

Usability of the Xuezhijing App

All participants were able to find sufficient room (approximately 2 m × 2 m) to perform the app guided exercise and were able to use the system after brief instruction. No technical issues (malfunctions in the Xuezhijing app and heart rate monitor device) was reported during the intervention.

All 19 participants filled out the uMARS scale. Scales were collected fully without any missing items; the score distribution is shown in Figure 3.

The overall objective quality uMARS score was 3.4 ± 0.7. Functionality was the objective domain with the highest rating (3.6 ± 0.8), which was followed by aesthetics (3.4 ± 0.8) and information (3.4 ± 0.8). The engagement subscale had the lowest rating (3.3 ± 0.7). The overall subjective quality uMARS score was 3.3 ± 0.6. The perceived impact rating was 3.7 ± 0.8 (Table 2).

Five (26.3%) participants provided a further narrative review regarding the Xuezhijing app. Four suggested "improving the heart rate chest belt" or "replacing the belt with wrist or arm band." One participant suggested "adding background music function." One expressed that "the program contributed to aid post-operation cardiac rehab and form exercise habit."

Adverse Events

Face to face clinical interviews and physical examinations were arranged for the participant who complained that wearing the chest belt was uncomfortable, and exercise related dyspnea or angina was ruled out.

No intervention related cardiovascular, cerebrovascular, or musculoskeletal adverse events were reported during the 12-week intervention.

Blood Lipids and Mental Health

Although this was a feasibility study, we conducted a preliminary analysis of lipid profile and mental health.

One participant did not undergo blood lipid testing at the 4-week checkpoint, because of the COVID-19 prevention policy; thus, the relevant data were excluded from related analysis. As shown in Table 3, the blood lipid levels at baseline were as follows: LDL-C 2.9 ± 0.8 mmol/L, TC 4.9 ± 1.3 mmol/L, TG 1.8 ± 1.2 mmol/L, and HDL-C 1.1 ± 0.3 mmol/L. The mean values of LDL-C and TC deceased after the intervention, whereas mean HDL-C level increased. The mean TG level decreased at the 4-week follow up, then increased at 12 weeks post intervention.

Shapiro-Wilk test indicated that the difference in LDL-C (4 w versus baseline, 12 w versus baseline, and 12 w versus 4 w), TC (4 w versus baseline, and 12 w versus baseline), and TG (4 w versus baseline) conformed to a normal distribution. Further paired T-tests indicated that LDL-C levels had significantly decreased at the 4-week and 12-week follow up, with respect to the baseline (-1.5 ± 0.8 mmol/L, $P < 0.001$, -1.6 ± 0.8 mmol/L, $P < 0.001$, respectively). TC had decreased significantly at the 4-week and 12-week follow up, with respect to the baseline (-1.8 ± 1.2 mmol/L, $P < 0.001$, -1.6 ± 1.3 mmol/L, $P < 0.001$, respectively), whereas TG had not (4 w versus baseline, $P = 0.21$).

Score distribution across uMARS items

■ Objective quality ■ Subjective quality ■ Perceived impact
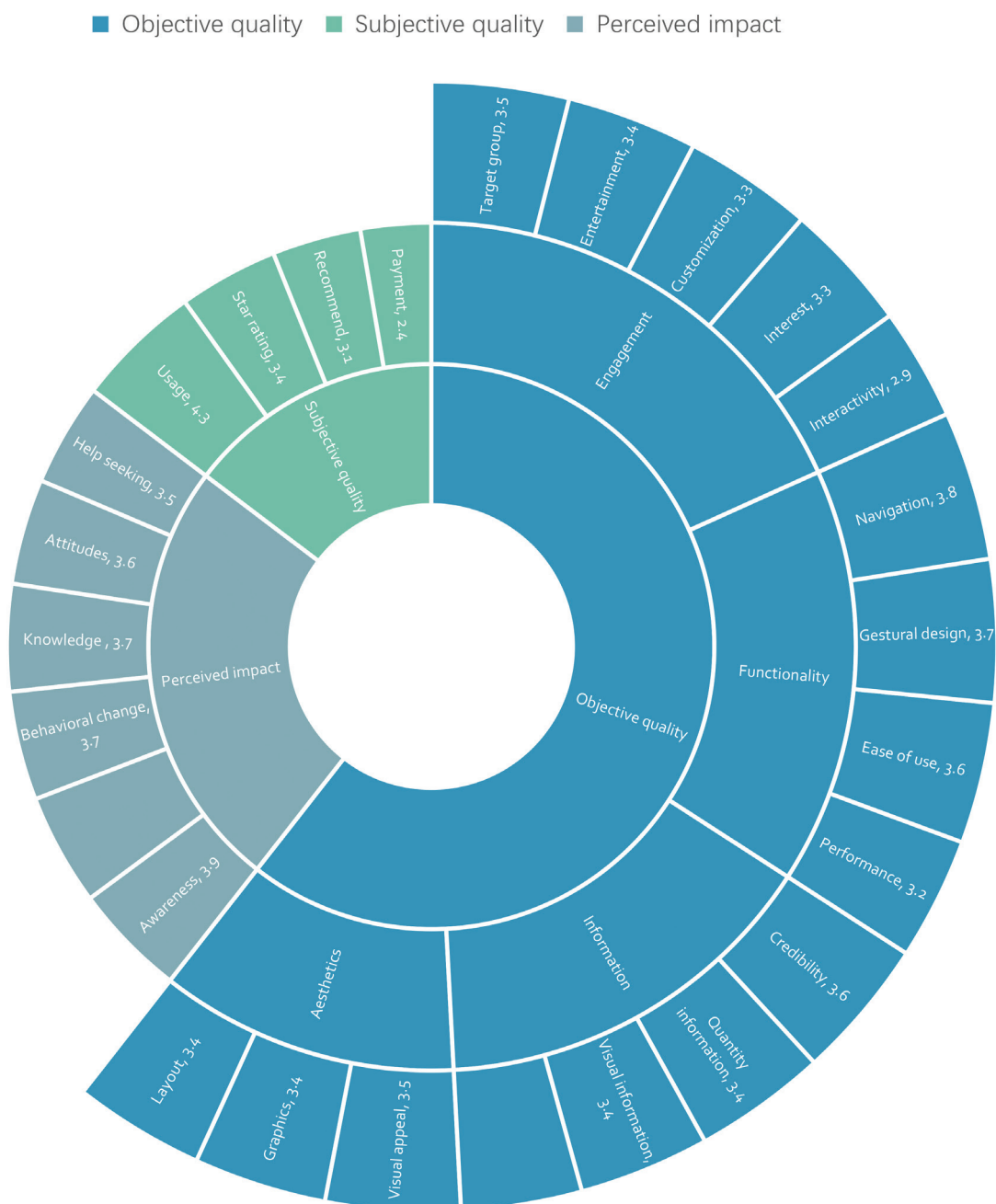
Figure 3 Sunburst Graph Showing Score Distribution Across uMARS Items.
Among objective subscales, the interactivity item received the lowest score, 2.9 ± 1.0. The payment item under the subjective quality subscale received the lowest score, 2.4 ± 1.2. The mean scores for the rest of the items were all above 3.

For the parameters that did not conform to a normal distribution, we further performed nonparametric tests on the lipid data. Results of two-independent-sample Wilcoxon tests showed significant differences in LDL-C and TC data measured at the 4-week and 12-week follow up, with respect to baseline levels (P < 0.001), whereas the comparison of other lipid data did not indicate significant differences.

Table 2 uMARS Scores Across all Subscales.

Subscale	Score
Objective quality	
Engagement	3.3 ± 0.7
Functionality	3.6 ± 0.8
Aesthetics	3.4 ± 0.8
Information	3.4 ± 0.8
Objective quality total	3.4 ± 0.7
Subjective quality	3.3 ± 0.6
Perceived impact	3.7 ± 0.8

Table 3 Blood Lipids Across the Study Timeline.

	Baseline	4 w follow up	12 w follow up
LDL-C	2.9 ± 0.8	$1.4 \pm 0.8^*$	$1.3 \pm 0.7^*$
TC	4.9 ± 1.3	$3.0 \pm 1.0^*$	$3.2 \pm 1.2^*$
TG	1.8 ± 1.2	1.6 ± 1.2	2.0 ± 2.8
HDL-C	1.1 ± 0.3	1.1 ± 0.5	1.3 ± 0.7

N = 19 for baseline and 12-week follow up blood lipid test results. N = 18 for 4-week follow up blood lipid test results. LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.
*Paired T test indicated a significant difference with respect to baseline, $P < 0.001$.

Mental Health

The mean GAD-7 score at baseline was 10.1 ± 4.1. The mean PHQ-9 score at baseline was 12.2 ± 3.9. Both mean scores had decreased in follow-up tests, as shown in Table 4. Independent samples Kruskal-Wallis test results indicated significant differences in GAD-7 and PHQ-9 scores across the study timeline ($P = 0.649$, $P = 0.140$, respectively).

Discussion

Feasibility of the Integrated Intervention

Participation rates in CR programs are far from satisfactory. One of the most important barriers is the inconvenience of transportation to treatment centers, particularly for employed patients. In 2017, more than 30 organizations launched the Million Hearts initiative, aiming to increase CR enrollment rates from 20% to 70% [6]. Beyond strategies to improve referral and enrollment, programmatic adaptations to deliver care efficiently and effectively were considered key to achieving the goal. These adaptations included the use of a hybrid model with on-site coordination of home programs and mobile monitoring technologies. This finding inspired us to design an integrated intervention program combining pharmaceutical and exercise intervention, and linking in-hospital healthcare with home-based programs. The program, given its pragmatic nature and near real world practice settings, had a retention rate of 76%. Therefore, we believe that this program has the potential to contribute to increasing the CR enrollment rate. The dropout rate in our study was primarily due to discomfort in wearing the heart rate chest belt, as reported by one participant. This finding highlights the importance of ensuring participant comfort and satisfaction with wearable devices in future interventions.

Adherence to the exercise component of the program was satisfactory; participants completed a total of 1336 exercise sessions over the 12-week period. The total exercise duration and the proportion of exercise performed within the prescribed intensity were also encouraging. These findings suggested that participants were willing and able to engage in regular exercise as part of the integrated intervention.

As recommended by guidelines [8, 9], eligible home-based CR program candidates were all pre-stratified into low to moderate risk groups; therefore, real time electrocardiographic monitoring was unnecessary and would have increased labor costs. Exercise was guided by in-app video, and exercise heart rate was monitored asynchronously, so that app users could conduct sessions freely; this aspect might have improved the flexibility and decreased

Table 4 GAD-7 and PHQ-9 Scores Across the Study Timeline.

	Baseline	4 w follow up	12 w follow up
GAD-7	10.1 ± 4.1 (8.1, 12.0)	8.6 ± 2.1 (7.5, 9.6)	9.1 ± 2.5 (7.9, 10.3)
PHQ-9	12.2 ± 3.9 (10.3, 14.1)	10.5 ± 1.7 (9.7, 11.3)	11.4 ± 1.9 (10.4, 12.3)

PHQ-9: Nine-item Patient Health Questionnaire; GAD-7: Seven-item Generalized Anxiety Disorder scale.

caregivers' workloads. The time commitment of the intervention was reasonable, with an estimated total management time of 65.47 minutes per patient over the 12-week period, including provision of initial instructions, messaging, inquiries, phone consultations, and exercise log checks. These time commitments are feasible for both participants and healthcare providers, thus making the intervention easily scalable and implementable in real-world settings. One medical staff member working 8 hours per day 5 days per week could manage 440 patients with ASCVD simultaneously.

The acceptability of the program was high: all participants provided satisfaction ratings on a Likert scale, and the mean score of satisfaction was 4.2 of 5, thus indicating that participants were generally satisfied with the intervention. However, 3/19 participants chose to discontinue alirocumab treatment after the first injection. We believe that greater patient choice over treatment modalities is a major factor contributing to the high satisfaction.

Additionally, the usability of the Xuezhijing app was good: all participants were able to use the app without any reported technical issues. The uMARS scores further supported the usability and subjective quality of the app, although participants provided suggestions for improvement, such as replacing the heart rate chest belt with alternative devices or adding background music functionality. Itemized uMARS analysis showing the "payment" item under subjective quality subscale received the lowest score of 2.4 ± 1.2, and the objective quality item "interactivity" under the engagement subscale received a score of 2.9 ± 1.0; these items were the only two below the acceptable threshold. CR enrollment costs in China have not been covered by public or commercial insurance, and people often have a limited understanding of cardiac rehabilitation. Patient willingness to pay remains a challenge until the issue of who will pay is resolved. During this research, we used a commonly used IM app and telephone as instant communication tools, whereas the app was used only to guide the exercise process; this aspect might have negatively affected the engagement experience.

Importantly, no intervention-associated adverse events were reported throughout the 12-week period. Thus, the integrated intervention appeared to be safe for patients with ASCVD and did not pose any additional cardiovascular or musculoskeletal risks.

Possibility of Quantifying Adherence to a Home-Based CR Program

Drawing conclusions regarding whether HBCR programs have superior adherence is difficult, because of variations in how adherence is reported [8]. Moreover, quantifying and evaluating exercise adherence similarly to how drug doses are calculated is difficult. Exercise intensity is a core component of CR guidelines, and is key to balancing health gains against cardiovascular risk. Exercise intensity is usually prescribed in the form of a heart rate range. With further development of technology, some quantifiable exercise executive parameters may become easier to collect through heart rate sensors, such as the HR physical activity score [13] introduced by Miller and colleagues, on the basis of cumulative heart rate increases in the time dimension or the EET parameter used in our study.

The EET setting was designed not only to log exercise more accurately but also to aid in real-time exercise intensity guidance. The exercise time on the patient's screen ticks only when the heart rate is in the physician's prescribed zone; otherwise the app gives voice and screen display reminders, so that users know whether they should slow or accelerate their pace to maintain the ideal cardiovascular load.

The mean EET per week was approximately 152.8 minutes, reaching the lower exercise limit recommended by guidelines [14, 15]. However, some patients were non adherent, and five patients quit the program without providing any feedback. We consider cultural factors to be an important factor in adherence, because patients in China might be relatively unlikely to refuse a physician's request in person, according to our experience. However, more work in the future should be devoted to improving the quality of patient education, building more healthy relationships between healthcare providers and patients, and improving the quality of medical services.

Preliminary analysis of blood lipid levels showed promising trends. Both LDL-C and TC levels had decreased significantly at the 4-week and 12-week follow-up, with respect to baseline levels. HDL-C levels increased over time, whereas TG levels

fluctuated without significant differences. These findings indicated potential improvements in lipid profiles with the integrated intervention, in agreement with findings from previous studies demonstrating the effectiveness of alirocumab in lipid-lowering [2].

Regarding mental health outcomes, our results indicated a downward trend in GAD-7 and PHQ-9 scores over time, although these changes were not statistically significant. This finding may suggest potential positive effects of the intervention on mental well-being; however, further investigation with larger sample sizes may be necessary to confirm these findings.

Interaction Between Alirocumab and Digital Exercise Prescription

The biweekly frequency of alirocumab decreased the amount of medication taken daily, but the long intervals between treatments require special reminders to avoid missing doses. With its in-app medication reminder module, the Xuezhijing app may be well suited to alirocumab. The integrated treatment approach enabled caregivers to have more interaction with patients, to reinforce education in a healthy lifestyle [8]. In this study, 84.2% of participants adhered to the alirocumab treatment schedule. LDL-C level is a key observational parameter in ASCVD management [16]. In this study, participants' LDL-C levels decreased by 62.1% and 55.2% at the 4-week and 12-week checkpoints, respectively, and were comparable to those in a representative clinical trial of alirocumab [17].

We also observed high variability in EET and the weekly exercise goal completion rate. Of the 19 participants, three did not achieve their weekly goals at all. One had exercised for 4729.1 minutes in 48 sessions without reaching the prescribed training intensity, although the participant's LDL-C levels decreased by 81.2% and 74.0% in the 4th week and 12th week, respectively, probably because the six doses of alirocumab were injected on schedule. Another participant receiving all six doses of alirocumab had an EET of 234.6 minutes, the lowest among the cohort, and was the only participant whose LDL-C had increased by 12.5% and 25% at the 4th and 12th weeks with respect to baseline, respectively. In the three participants who received only one dose of alirocumab, the total EET reached 2357.9 ± 293.6 minutes, and the LDL-C levels decreased by 46.9% ± 26.4% and 43.7% ± 30.7% at the 4th and 12th weeks, respectively. These findings suggested that alirocumab plus exercise might be beneficial for LDL-C control in patients with ASCVD, and even mild exercise may also contribute. Because of limitations due to the small sample size, we plan to further explore the interactive effects of alirocumab and digital ERx in a future full-scale study.

In this study, in contrast to other exercise intervention studies [18], participants' mental health status did not change significantly. The small sample size prevented meaningful deeper investigation of the cause, but the influencing factors might include relatively low baseline anxiety and depression levels, in the context of the COVID-19 pandemic.

Limitations

We designed this study to test the feasibility of our integrated program. First, the small sample size should be considered in evaluating the effectiveness parameters. Second, participant dropout and loss of contact occurred during the study, thus potentially introducing selection bias and affecting the interpretation of our results. Despite efforts to reach out to the participants, unsuccessful contact attempts hindered complete follow-up data collection. Third, the duration of the intervention was limited to 12 weeks. Longer-term follow-up would provide valuable insights into the sustainability and durability of effects beyond this initial period. Finally, all participants in our study were recruited from a single center, thus potentially limiting the generalizability of our findings to a broader population. Future studies should consider multi-center collaborations or include participants from diverse settings to enhance external validity. These limitations highlight areas for improvement and emphasize the need for larger-scale studies with more rigorous designs. Despite these limitations, our study provides preliminary evidence supporting the feasibility of our integrated program.

Conclusion

Overall, our results indicate that an integrated intervention program featuring alirocumab combined with home-based digital ERx powered by the Xuezhijing app is feasible and acceptable among patients with ASCVD. The program demonstrated

high retention rates, satisfactory adherence to exercise prescription, reasonable time commitments, good acceptability and usability of the app, and potential improvements in lipid profiles. Further larger-scale studies are warranted to validate these findings and assess long-term outcomes.

Data Availability Statement

The data supporting the findings of this study are available from the authors with the permission of Shaorong Wu and First Affiliated Hospital of Jinan University, on reasonable request.

Ethics Statement

This study was conducted in accordance with the ethical standards established by the Research Ethics Review Committee of the First Affiliated Hospital of Jinan University. All participants provided written informed consent, and the study protocol was approved by the Research Ethics Review Committee of the First Affiliated Hospital of Jinan University under protocol number KY-2021-085.

Author Contributions

Conceptualization and Methodology, Shaorong Wu and Yi Xu; Recruitment and intervention, Weiyu Qiu, Jianwei Chen and Xianwu Lan; Data Analysis, Yan Li; Writing, Yi Xu; Review & Editing, Shaorong Wu.

Funding

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgements

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