The University of Hong Kong
School of Nursing

Research Protocol

Study Title: An internet-based cardiac rehabilitation enhancement (i-CARE) intervention to support self-care of patients with coronary artery disease: A mixed-method study

Background

Cardiovascular diseases (CVD), the leading cause of death globally, remains a significant and ever-growing public health concern in every region of the world.[1,2] Advancements in CVD diagnosis and treatments and increasing life expectancy have resulted in high prevalence of patients living with CVD, who are at high risk of morbidity and mortality.[3] The majority of CVD deaths are attributed to an acute manifestation of coronary artery disease (CAD), defined as narrowing of coronary arteries that causes insufficient myocardial blood flow due to accumulation of atherosclerotic plaque.[4] CAD has reached an unequivocal pandemic status globally and locally, imposing not only significant physical and psychosocial burdens on patients, but also enormous service demands on the healthcare systems. Recent local statistics reported that CAD was responsible for 34,000 hospital admissions per year (i.e., 93 admissions per day).[5] Moreover, a cost-of-illness analysis revealed the mean first-year total direct medical expenditure associated with a newly diagnosed stable CAD patient in Hong Kong was up to US$11,477.[6] This substantial disease burden on healthcare is expected to increase further with inevitable trend of ageing population and increasing life expectancy.[7]

In response to changes in the epidemiology of CAD, existing care efforts are directed towards the provision of emergency services to patients during acute disease manifestations (i.e. acute myocardial infarction) and cardiac rehabilitation following revascularization procedures.[8] There is a lack of proactive care for patients with mild to moderate CAD who have not yet developed an acute exacerbation, representing a major service gap, or "missing piece". These patients account for two thirds of all acute myocardial infarction, despite having coronary artery stenosis levels of <50%.[9] In addition, an episodic, acute care remains a major focus of our healthcare system, whereas secondary prevention of CAD cultivated by effective risk factor management and self-care receive inadequate attention.[10] Therefore, it is crucial to fill this "missing piece" in the CAD management continuum in order to reduce morbidity and mortality in patients with established CAD.

The priority of care for CAD is to delay the progression of coronary arterial occlusion and improve prognosis through pharmacological and non-pharmacological means to control the modifiable risk factors, including lifestyle behaviours. Viewing the chronic nature of CAD, it requires patients to practice persistent self-care in a long-term manner for successful disease management.[11] Self-care is defined as the ability of individuals to engage in the decision-making process for the purpose of maintaining health and managing his/her chronic health conditions.[12,13] Effective self-care has been consistently identified in empirical studies as the most cost-effective means of achieving disease management goal and is considered fundamental to the prevention and management of chronic diseases.[12] The concept of self-care of chronic illness comprises three core elements: self-care maintenance, self-care monitoring and self-care management. Self-care maintenance requires adherence to behavioral modifications to maintain physical and emotional stability, whereas self-care monitoring and self-care management refer to self-observation of signs and symptoms and response to the observed signs and symptoms respectively.[12] In the context of CAD, self-care actions including lifestyle modifications such as maintenance of a healthy diet and physical activity, medication adherence, control of risk factors such as blood glucose for diabetes and blood pressure for

hypertension, self-monitoring of symptoms indicating disease deterioration (e.g., chest pain, dyspnea), and appropriate responses to these symptoms, are efficacious in reducing the risk of future cardiovascular events and death.[11,12] Despite the strikingly proven clinical benefits of persistent self-care interventions as an effective secondary preventive measure for CAD, only a small proportion of patients achieved a satisfactory control of risk factors.[14] The underlying reasons for non-adherence to self-care behaviors are multifactorial, involving system-related and patient-related factors that hinder patients' motivation and participation.[15] To promote self-care among patients with chronic conditions such as CAD, healthcare providers have most commonly adopted didactic education modalities focusing on the provision of information and knowledge regarding self-management.[16] However, this didactic, unidirectional approach appears to be failing and has been widely criticized as insufficient in terms of encouraging internal motivation for achieving behavioral changes.[17] Furthermore, the participation and completion rates of conventional face-to-face educational programs are low.[18,19] Scheduling problem, shortcomings of the healthcare system and limited geographical accessibility play a pivotal role in non-participation.[19] In addition, enabling people to initiate and sustain behavioral changes to adopt a heart-healthy lifestyle remains a major challenge. In light of the limited participation of health promotion activities and suboptimal control of risk factors, it is imperative to develop a more effective alternative to enhance self-care and achieve secondary prevention in CAD patients.

To foster behavioral change for better control of risk factors and disease management among CAD patients, a plethora of studies have suggested that bolstering patients' self-efficacy and assisting them to overcome the barriers of self-care are the most salient strategies.[20-24] Self-efficacy is a psychological construct based on Social Cognitive Theory, which provides a blueprint for producing desirable behavioral changes related to lifestyle modifications, whereas long-term behavioral maintenance is of particular importance.[20,24] Social Cognitive Theory posits that apart from enhancing people's knowledge, emphasis should be placed on boosting self-efficacy through reviewing previous successful performance of tasks (mastery experiences), observing others who have conquered a task (vicarious experiences), and being persuaded by others regarding their capacities to perform a specific behaviour.[25] Studies have demonstrated that patient self-efficacy and engagement in self-care are salient factors of satisfactory risk factor control and disease management in CAD, and patients with higher level of perceived ability to self-manage their CAD showed improved health behaviors and clinical outcomes including quality of life.[23,26-30] Given the profound effects of self-efficacy on improving self-care of patients, an effective secondary prevention programme should therefore incorporate the aforementioned strategies to facilitate self-care and promote sustained behavioral change among CAD patients.

Lately, digital health interventions involving the use of information and communication technology for secondary prevention among CAD patients has evolved as a promising alternative to traditional face-to-face cardiac rehabilitation services. An estimated of 54% of the world's population is using internet, whereas in Hong Kong, almost 90% of people are internet users.[31,32] Given the proliferation of internet and wide availability of smartphones in recent years, mobile technology has been gaining popularity in the delivery of secondary prevention programmes. Mobile technology provides an automated platform that allows instant retrieval of health information, with the capacity to incorporate education, motivation, reminders and support to promote self-care.[33,34] In addition, in view of the recent coronavirus disease 2019 (COVID-19) pandemic, the government has put forth a series of measure to contain the spread of this disease, of which social distancing and gathering limit remain the foremost strategy. All these regulations have hampered the provision of face-to-face health promotion services and rendered this conventional mode of service delivery to be less feasible and unfavourable. This novel infectious disease with uncertain trajectory has accentuated the

need to develop innovative care-delivery strategy, so as to address the social and care needs of patients even in the face of the unprecedented times of global crisis. Using mobile technology to support health maintenance is highly feasible in this digital era where smartphone and internet are highly accessible. Mobile technology is able to bridge time and distance barriers to clinical oversight and expand accessibility to care which is traditionally delivered face-to-face, therefore, potentially fill in the evidence-practice gaps in cardiovascular care.

Recent systematic reviews have provided substantial evidence to support the feasibility and beneficial effects of internet- or smartphone-delivered interventions on self-care among CAD patients.[34-39] Components of these intervention included risk factor control, physical activity promotion, health education on CAD and its management, and medication adherence enhancement. These reviews showed that personalized interventions with persuasive techniques, such as self-tracking, goal-setting, feedback and reminders were effective to engage CAD patients in healthy lifestyle behaviours, as reflected by improved self-reported, physiological and anthropometric outcomes such as medication adherence, blood pressure and body mass index (BMI).[34-39] Despite these encouraging findings, several methodological limitations of previous studies may threaten the validity of the results. Firstly, there were studies using exclusive subjective measures for outcome evaluation,[40-45] therefore, self-reported outcomes are highly subject to biases. Moreover, some studies incorporated anthropometric and laboratory metrics for outcome evaluation, such as BMI.[45-47] Indeed, empirical evidence has suggested that cardiometabolic risk is strongly associated with visceral adiposity, instead of body weight per se.[48] As such, laboratory and anthropometric markers indicative of visceral adiposity are suggested to evaluate the effects of lifestyle interventions rather than BMI alone.[49] Secondly, a vast majority of previous internet-based interventions mainly targeted at reducing conventional CAD risk factors such as high blood pressure and smoking, while novel lifestyle risk factors received inadequate attention. For instance, sleep quality and psychological stress were often being neglected. Studies are emerging to suggest sleep disturbance as an independent lifestyle risk factor for CAD,[50,51] yet an overwhelming majority of previous studies did not include a component to improve sleep. Similarly, psychological stress is well-recognized as an independent cardiometabolic risk factor,[52] but there were only few studies included psychological symptoms as secondary outcomes.[44,47] Most of the previous internet-based interventions failed to demonstrate an effect on psychological outcomes among CAD patients. In view of the high prevalence of psychological stress and poor sleep among the CAD population,[53-55] more research is warranted to address these significant risk factors in the future. Although the reported findings of previous studies were relatively consistent, the mechanisms of how these complex interventions work remain unclear, underpinning the need for the development of comprehensive care framework to understand the cognitive and psychological processes among CAD patients.

Furthermore**,** many of the previous studies adopted a "one-size-fits-all" approach, which is, providing standardized package of educational contents regarding CAD risk factor that patients possess in general, regardless of their individual characteristics and disease background when designing their secondary prevention interventions for CAD patients.[45,56-62] This large volume and high complexity of health information can put patients at risk for information overload.[63] A study examining the effect of information overload among patients with CAD found that patient with higher level of perceived information overload were more likely to be confused and this had a direct negative impact on their intentions to read self-care educational materials and interact with healthcare providers.[64] Different CAD patients would experience unique risk factor profiles, a personalized educational content that are tailored to individual characteristics, preferences and needs are essential to make the health messages more salient to patients and increase the effectiveness of health education to promote self-care and bring about behavioural change.[63] However, there is currently a paucity of research on this ground either in Europe,

Asia or Hong Kong. With a view to address the cultural differences across countries and enhance the generalizability of findings to local population, there is therefore a pressing need to develop a customized, adaptive and sustainable secondary prevention intervention tailoring to individual risk factor profiles among CAD patients. The increasing use of mobile technology offers an optimistic prospect for offering CAD patients a culturally compatible interventions that accommodate their information needs and enhance self-care.

Given the robust evidence indicating the benefits of consistent self-care for CAD patients, there is a desperate need to identify effective and feasible interventions to optimize the care of this burgeoning population. With increasing evidence suggesting the beneficial effects of internet- and smartphone-based interventions on promoting self-care in CAD patients, it is timely to reduce the current evidence-practice gaps of suboptimal secondary prevention in this clinical cohort, particularly those not eligible for routine cardiac rehabilitation. This first-ever local study plans to develop a theory-guided, internet-based self-care support intervention in the format of a mobile application, entitled "internet-based CArdiac Rehabilitation Enhancement (i-CARE)", for promoting self-care of patients with CAD. The intervention will eschew the traditional one-size-fits-all approach, instead, it will address the individualized risk profiles and comprehensive needs of the CAD patients who are routinely excluded from traditional cardiac rehabilitation.

Research plan and methodology

The proposed study will have two aims: 1) to evaluate the effects of i-CARE on self-care behaviors, blood pressure, waist-to-height ratio, cholesterols, functional status, health-related quality of life (HRQoL) of CAD patients, and 2) to explore how and why i-CARE affects the health behaviors from the patients' perspective.

Study design

This mixed-method study consists of a single-blinded two-arm randomized controlled trial (RCT) to examine the effects of the i-CARE program on behavioral and cardiovascular outcomes in CAD patients, and an exploratory qualitative study to explore participants' perceived benefits, challenges and limitations of the i-CARE program. This study will recruit eligible participants from the cardiac clinics and wards of two regional hospitals in Hong Kong.

Study participants

Adults will be eligible to join the study if they are: 1) living in the community, 2) owning a smartphone with internet access, 3) communicable in Cantonese, 4) able to type in Chinese or English, and 5) with a confirmed diagnosis of CAD. Individuals will be excluded if they have: 1) enrolled to a structured center-based or home-based cardiac rehabilitation programme in the past year, 2) known psychiatric problems, 3) impaired cognitive functioning (i.e. Abbreviated Mental Test $\leq$6), and 4) terminal disease with life expectancy < 1 year.

For the RCT, the sample size is determined on the basis of a systematic review that identified small to medium effect sizes (0.42–0.66) of information and communication technology-based cardiac rehabilitation on health behaviors among patients with CAD.[65] This study will conservatively assume an effect size as 0.4. The power analysis software PASS 14 (NCSS, Kaysville, UT) estimated that a sample size of 100 subjects per study group would give the proposed two-arm randomized controlled trial 80% power at a two-sided 5% level of significance to detect an effect size of 0.4 on the primary outcome between the control and intervention groups at the post-intervention time point. After allowing for a potential dropout rate of up to 25%, 268 subjects (i.e. 134/group). For the qualitative phase, a criterion sampling of 30 participants who have received the i-CARE program will be invited to join on the basis of their post-intervention changes in the primary outcome, with 10 participants from each

category (low, medium and high percentile). Maximum variations in the participants' sociodemographic and clinical characteristics will also be considered in the sampling procedure to ensure a wider range of data.

Randomization and blinding

After collecting baseline data, the research nurse will randomly allocate patients into the intervention or control group. Block randomization (block size: 8, 10, or 12) will be used to ensure even participant distribution between the two groups. The block size and respective study group allocation sequence will be determined using a computer-generated sequence. Chronologically recruited patients will be allocated to the study groups by the nurse according to this computer-generated sequence. Participants allocated to the intervention group will receive the i-CARE intervention, while those allocated to the control group will continue to receive conventional care as arranged by the hospital. An independent research assistant who is blinded to study group allocations will collect post-intervention data.

Intervention group: i-CARE

Participants in the intervention group will receive a 12-week i-CARE intervention, which will be designed to cover the core elements of CAD self-care: self-care maintenance, self-care monitoring and self-care management. The intervention will comprise: 1) a single individualized face-to-face session and 2) an internet-based intervention through a mobile application, which is developed by the investigation team of this project. Various behavior change techniques will be used to increase the self-efficacy of CAD patients in enacting self-care behaviors. The details of these two care components are described as follow.

1) Face-to-face orientation session

   This single face-to-face session serves to orientate and prepare participants to actively engage in the upcoming internet-based intervention. The research nurse (RA1) will highlight the crucial role of patients themselves in managing the disease by assisting them to understand the links between their self-care behaviors and health consequences. A subsequent interactive skill-building session to ensure patients acquire the skills required for performing self-monitoring techniques, including blood pressure, heart rate and blood glucose measurement. The participants will be required to perform return demonstration to ensure skill acquisition. The nurse will then introduce the mobile application and assist the participants to register an account. Upon successful registration, a password will be provided. He/she will demonstrate the key functions of the application and assist the participant to personalize the setting according to their individualized risk profile and preferences. The nurse will emphasize the importance of compliance to self-care behaviors and will facilitate the participants to set self-directed goals at the end of this session.

2) Internet-based intervention via a mobile application

   The mobile application will consist of three key user interfaces, including the self-monitoring dashboard, the interactive self-care modules and the chat room. A group of 12 CAD patients with diverse socio-demographic background will be invited to test the user interface. Their comments will be incorporated to optimize the design, content, layout and visual features before the application is formally launched for testing.

   The self-monitoring dashboard is a personalized interface that allows participants to select relevant parameters for regular self-monitoring according to their own risk profile, which include blood pressure, heart rate, lipid profile and blood glucose. In addition, the physical activity levels of each participants will be monitored with a pedometer. The

number of steps will be synchronized to the dashboard regularly. All parameters will be self-measured and entered to the dashboard by the patients on a daily or weekly basis except lipid profile, which will be entered by the research nurse according to the results extracted from the Clinical Management System. The participants can customize the application features on receiving notifications and motivational messages. The input data will be presented in a graphical format to visually demonstrate the changes over time.

The interactive self-care modules will cover the following topics: 1) CAD, its symptom monitoring and management, 2) medication management, 3) personalized risk factor control (e.g. body weight reduction, smoking cessation, blood pressure control, glycemic control, lipid control, and insomnia), 4) healthy diet, 5) activity and exercise, and 6) stress management. The contents of this module are consistent with the recommendations of major international guidelines on CAD management.[66] A variety of interactive features will be used to improve engagement, motivation and knowledge acquisition of the participants, including the use of audio-visual format with animations and illustrations, peers with successful self-care experience will also be invited to share the tips with the participants. The participants will be guided to establish an individualized action plan, which an exhaustive list of actions in categories will be presented for the participants to select those actions according to relevancy and preferences.

The chat room will serve as a platform to facilitate the nurse to provide coaching to motivate and facilitate behavioral changes of the participants. The nurse will review the self-monitoring data and keep track on the progress of goal attainment of each participant. He/she will initiate chatting with the participants in this platform weekly, to identify any problems that the participants encountered in their daily practice of self-care behaviors, and will explore the underlying barriers, then advise resolving methods to minimize the barriers and improve adherence. Health counselling and advice given will be documented to guide subsequent communication. Throughout the process, the nurse will adopt therapeutic communication skills, and a supportive and non-judgmental attitude. The participants can also initiate the communication with the nurse in the chat room regarding disease management. The nurse will offer advice and counselling accordingly during office hours. An automatic system-generated message will pop up to remind the participants to seek urgent medical care for newly onset symptoms that may suggestive of disease exacerbation or deterioration.

<u>Control group: Usual care</u>

The control group will continue to receive conventional care as arranged by the hospital. They will not receive any structured cardiac rehabilitation interventions during the study period.

<u>Fidelity monitoring of the study intervention</u>

To optimize fidelity of the study intervention, a training manual will be used to guide the intervention delivery. The research nurse (RA1) will receive two weeks of comprehensive training from the investigation team on CAD, principles and skills in patient education, methods to deliver the study protocol and counselling via the chatroom. For fidelity monitoring, the principal investigator will randomly select 10% of the face-to-face educative sessions for fidelity monitoring. The educative sessions will be audiotaped with the participants' consent, the chat record between the research nurse and participants in the chatroom will be reviewed. Thirdly, the login activities, number of completed sessions, the self-monitoring dashboard activities of all participants will be tracked. All of these data will be used to interpret the RCT findings.

Outcome measures

Primary outcome

Self-care behaviors:

The Chinese version of Self-Care of Coronary Heart Disease Inventory (SC-CHDI) will be used to measure self-care behaviors. This self-reported SC-CHDI (22 items) measures self-care maintenance, self-care management and self-care confidence on a four-point response scale. Each subscale score is transformed to 100 points, with higher scores indicate better self-care for that attribute. It has acceptable reliability (Cronbach's alpha: 0.76 – 0.87), good factorial and convergent validity.[67]

Secondary outcomes

Functional status:

The Chinese version of Seattle Angina Questionnaire will be used to measure functional status. This 19-item questionnaire consists of five subscales, including physical limitation, angina stability, angina frequency, treatment satisfaction and the disease perception. The respondents have to rate on a 1 to 5 or 6 sequentially coded status. The subscale scores are transformed to a scale of 0 to 100, with higher scores indicate higher level of functioning/ satisfaction and fewer limitations. The Chinese version has been shown to be reliable, valid and sensitive to clinical change.[68]

Disease-specific health-related quality of life (HRQoL):

The Chinese version of MacNew will be used to measure disease-specific HRQoL.[69] It consists of 27 items measuring HRQoL in three domains (physical, emotional and social). Each item is rated on a 1-7 scale, and a global score is calculated by summing the item scores, a higher score represents better HRQoL. MacNew has been validated in Hong Kong Chinese, which indicated satisfactory internal consistency (Cronbach's alphas $\geq$ 0.87) and test-retest reliability, concurrent and discriminant validity.[69]

Physiological and biomarkers:

Physiological parameter (blood pressure), anthropometric measure (waist-to-height ratio) and biomarkers (lipid profile: total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) will be assessed/collected/tested according to standard protocol. The fasting lipid profile will be measured by a validated point-of-care machine. A capillary blood sample will be collected from a finger stick after 8 hours of fasting. Point-of-care testing has proved reliable and correlates well with the standard laboratory testing.[70]

Cardiovascular events and mortality:

The cardiovascular event rates and mortality data will be monitored after participant recruitment. The admissions, cardiovascular event rates and mortality data will be retrieved from the Clinical Management System by the research nurse, who will also ascertain any admissions to private hospitals. The same information will too be collected via patient's or family member's self-report.

Data collection procedure

After obtaining the approval from the respective ethics research committees, the research nurse will recruit eligible participants from the cardiac clinics and wards of two regional hospitals in Hong Kong. The local PI will identify potential subjects from the admission record and follow-up list of the cardiac ward and clinics respectively, and refer them to the research nurse. The research nurse will screen their eligibility according to the predefined criteria. All the eligible patients will be invited to participate. He/she will introduce the study to potential participants verbally, supplemented with a written information sheet. After obtaining the participants'

written informed consent, the nurse will collect socio-demographic and clinical data through patient's self-report and medical record review, while the nurse will assist participants to complete the SC-CHDI, SAQ and MacNew through a secured online platform Qualtrics. The physiological, anthropometric and biomarkers will be collected according to the standard protocol. The research nurse will then allocate the participants into intervention or control group by block randomization, to receive the i-CARE intervention or usual care, respectively. The post-intervention data will be collected through the mobile application, a message will be popped up to remind the participants at 3 and 6 months thereafter. A trained research assistant who has no knowledge of the group allocation, will be responsible for collecting the post-intervention physiological, anthropometric and biomarkers. A subsample of the participants will be invited to participate in the qualitative phase. Semi-structured interviews will be conducted by the principal investigator with an interview guide, which includes open-ended questions to enquire about their engagement experience in the intervention.

Data Analysis

For the RCT study, data analysis will be performed according to the intention-to-treat principle. Baseline characteristics between the two study arms will be compared by t-test, chi-square or Fisher's exact test as appropriate. The generalized estimating equation (GEE) model will be used to compare the differential changes on the outcomes across the time points T0, T1 and T2 between the two study arms with adjustment for potential confounding variables. Baseline characteristics with p values < 0.25 for between-group difference will be considered as potential confounding variables.[71] GEE model can account for intra-correlated repeated measures data and accommodate missing data caused by incomplete assessments or dropout, provided that the data are missed at random,[72] and thus are particularly suitable for intention-to-treat analysis without the need of imputation for missing data. All statistical analyses will be performed using IBM SPSS 25.0. All statistical tests will be two-sided and a p-value < 0.05 will be considered statistically significant. For the qualitative study, the audio-taped data will be transcribed verbatim. The principal investigator will ensure accuracy of the transcription by cross-checking. Content analysis will be adopted to code the qualitative data on participants' perceptions and acceptability of the technology-based self-care support intervention.[73] The analysis will also seek to understand why and how the study intervention influences patients' health behaviors. The codes will be organized into categories and subcategories, which will be analyzed for emerging themes. The trustworthiness of the qualitative analysis will be enhanced by audio-taping of the interviews, conducting an audit trail, involving two team members to code the qualitative data independently.[74]

Ethical Consideration

This study followed the Declaration of Helsinki on medical protocol and ethics. Ethics approval will be obtained from the respective research ethics committees of the study sites. The participation is absolutely voluntary in the study. A written informed consent, which will include the research title, background, purpose, the procedures and level of involvement will be fully explained to each potential participant. Risks and benefits of involving in this study will also be explained clearly to the participants. Participants will be assured for their right to withdraw from the study at any time, without giving a reason. They will be protected from discomforts and harms during the study. Further, anonymity and confidentiality of the participants will be strictly protected. Their decision of participating in the study will not affect the quality of present or future care they receive in the health and social care settings.

Personal data privacy protection and data security

The mobile application will be developed by the investigation team of this project with the assistance of a professional mobile application development company. Professional web services will be used to host the application, which it will provide the key features on data security, such as distributed denial-of-service (DDoS) protection, central management of firewall rules, threat detection and continuous monitoring, Secure Sockets Layer (SSL) / Transport Layer Security (TLS) management and so on. These features protects the application from common cyberattacks.

To protect the personal data privacy, a subject code will be assigned to each participant. Theie identifiable information (e.g., name, HKID number) will not appear on any data record sheets or the application. All the collected data will be stored in a password-protected, university-owned computer, and those hard copies will be stored in a locked cabinet in the School of Nursing, The University of Hong Kong. Confidentiality of the subjects' personal data will be protected according to the Personal Data (Privacy) Ordinance. They can enjoy this right for the protection of their personal data, such as collection, retention, management, use (including analysis or comparison), non-disclosure, erasure and/or in any way dealing with or disposing of any of their personal data in or for this study.

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