Circulation Reports
Circ Rep 2023; 5: 62–65
doi:10.1253/circrep.CR-22-0121

PROTOCOL PAPER

Study Protocol of Cardiac Rehabilitation for Acute Myocardial Infarction From the JROAD/JROAD-DPC Database

— JROAD-CR —

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Background: Although cardiac rehabilitation (CR) has been reported to be effective for improving the prognosis of acute myocardial infarction (AMI), more patients must participate in CR during admission and as outpatients. Factors contributing to, and countermeasures against, the low CR participation rate need to be identified. Here we describe the protocol for a study designed to evaluate the effectiveness and problems of CR for AMI from the Japanese Registry of All Cardiac and Vascular Diseases (JROAD) and the JROAD–Japanese Diagnosis Procedure Combination system (JROAD-DPC) database.

Methods and Results: This is a multicenter retrospective cohort study that will use the JROAD/JROAD-DPC database to evaluate the effectiveness of CR for AMI (JROAD-CR). Five thousand patients with AMI who were admitted to hospitals registered in the JROAD database in 2014 will be investigated with regard to their baseline characteristics, AMI severity and treatment, examination results, history of CR, and prognosis up to 5 years. We will also investigate the presence, quantity, and quality of CR, and evaluate the effectiveness of CR with respect to cost, exercise tolerance, and prognosis during admission and follow-up.

Conclusions: The JROAD-CR study will seek to reveal the effectiveness of CR for AMI in the era of early reperfusion therapy and shortened hospitalization.

Key Words: Acute myocardial infarction; Cardiac rehabilitation; Early reperfusion therapy; JROAD; Shortened hospitalization

Cardiovascular disease is a major cause of death in Japan and in other countries. Acute myocardial infarction (AMI) has the second-highest mortality rate among cardiovascular diseases in Japan.[1] Although early reperfusion therapy for AMI has improved mortality in the acute phase,[2] major adverse cardiovascular events (MACE) in patients with AMI remain a major problem.[3]

Cardiac rehabilitation (CR) has a Class I recommendation to improve exercise tolerance, quality of life, and prognosis for AMI during the recovery phase.[4] CR with care during the acute phase, exercise test at discharge, and a recommending CR for outpatients also have Class I rec-

Received November 24, 2022; revised manuscript received December 22, 2022; accepted January 6, 2023; J-STAGE Advance Publication released online January 25, 2023 Time for primary review: 24 days

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ISSN-2434-0790

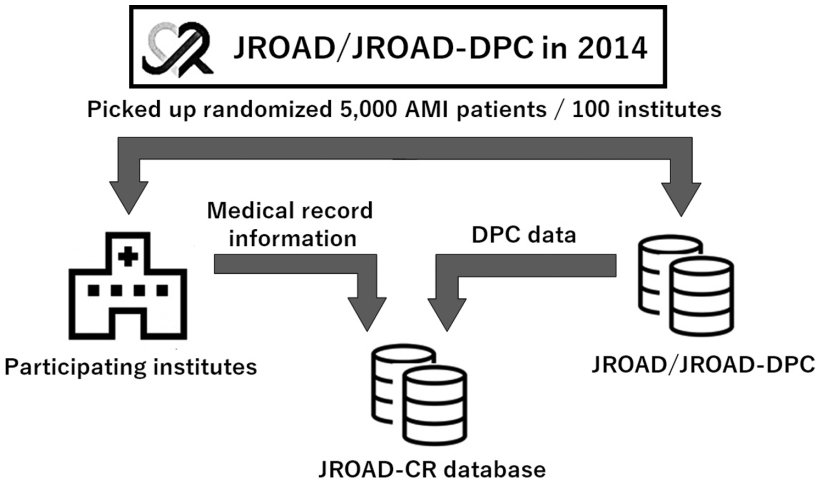


Figure 1. Study chart. AMI, acute myocardial infarction; DPC, Diagnosis Procedure Combination; JROAD, The Japanese Registry of All Cardiac and Vascular Diseases; JROAD-CR, JROAD/JROAD-DPC database to evaluate the effectiveness of cardiac rehabilitation for AMI.

ommendations.[4] However, the participation rate in outpatient CR for AMI remains low.[5] The Second 5-Year Plan for Overcoming Stroke and Cardiovascular Disease developed by the Japanese Circulation Society, the Japan Stroke Society, the Japanese Association of Cardiac Rehabilitation (JACR), and other related societies emphasizes the importance of CR from an early stage of treatment.[6] Although CR has been reported to be effective in improving the prognosis of AMI, we need to re-evaluate the effectiveness of CR for AMI and identify factors contributing to, and countermeasures against, the low participation rate of outpatients in CR in the era of early reperfusion therapy and a considerably shortened hospitalization period. We will also investigate the effectiveness of CR for all-cause death, because this issue remains controversial.[7–9]

The Japanese Registry of All Cardiac and Vascular Diseases (JROAD) and JROAD-Japanese Diagnosis Procedure Combination system (JROAD-DPC) were developed in 2014 by the Japanese Circulation Society. JROAD/JROAD-DPC is a nationwide claims database that contains all the data for cardiac inpatients admitted to JROAD-registered hospitals in Japan. The database includes information on age, sex, diagnosis, comorbidity, treatment (including procedures and medications), complications, hospitalization days, outcomes, and costs.[10] We will conduct a study using the JROAD/JROAD-DPC database to evaluate the effectiveness of CR for AMI (JROAD-CR). Herein, we present the study protocol for JROAD-CR.

Methods

Study Design

JROAD-CR will be a multicenter retrospective cohort study. AMI patients who were admitted to hospitals registered with the JROAD database in 2014 will be investigated. Information obtained from the database will include baseline characteristics, AMI severity and treatment, examination results, and CR history, and we will follow the prognosis for 5 years. The JROAD-CR database, which contains data from the JROAD/JROAD-DPC database, and the electronic data capture (EDC) system were developed by the JACR (**Figure 1**). We will investigate the presence, quantity, and quality of CR and evaluate the effectiveness of CR with respect to cost, exercise tolerance, and prognosis during admission and long-term follow-up. All procedures will be performed in accordance with the Declaration of Helsinki and the ethical standards of the Independent Review Board of Fukuoka University. The study protocol was approved by Fukuoka University Ethics Committee (No. U22-09-012) and the ethics committees of participating institutions. This study was approved to use a simplified informed consent by the Independent Review Board of Fukuoka University. This clinical trial has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000049490).

Subjects

Patients will be required to meet the following inclusion criteria: (1) age ≥20 years; and (2) having had an AMI and having been admitted to a hospital registered in the JROAD database in 2014. Patients who were admitted due to old myocardial infarction or recurrent myocardial infarction and patients who died during hospitalization will be excluded from the study.

Study Endpoints

The primary endpoint is the composite of MACE (cardiovascular death, non-fatal myocardial infarction, angina pectoris, hospitalization for heart failure, cerebral infarction, cerebral hemorrhage, pulmonary embolism, ruptured aortic aneurysm, aortic dissection, and fatal arrhythmia). Secondary endpoints are all-cause death, cardiovascular death, non-fatal myocardial infarction, hospitalization for heart failure, cerebral infarction, cerebral hemorrhage, costs, changes in body weight, blood pressure, smoking cessation, cardiac functions, laboratory examinations, and cardiopulmonary functions.

Statistical Analyses

Sample Size and Power Calculations Approximately 100,000 AMI patients were added to the JROAD/JROAD-DPC database in 2014. Five thousand AMI patients will be recruited from approximately 100 institutions, including all cases of AMI from the 19 institutions that have been certified for CR training by the JACR. For institutions

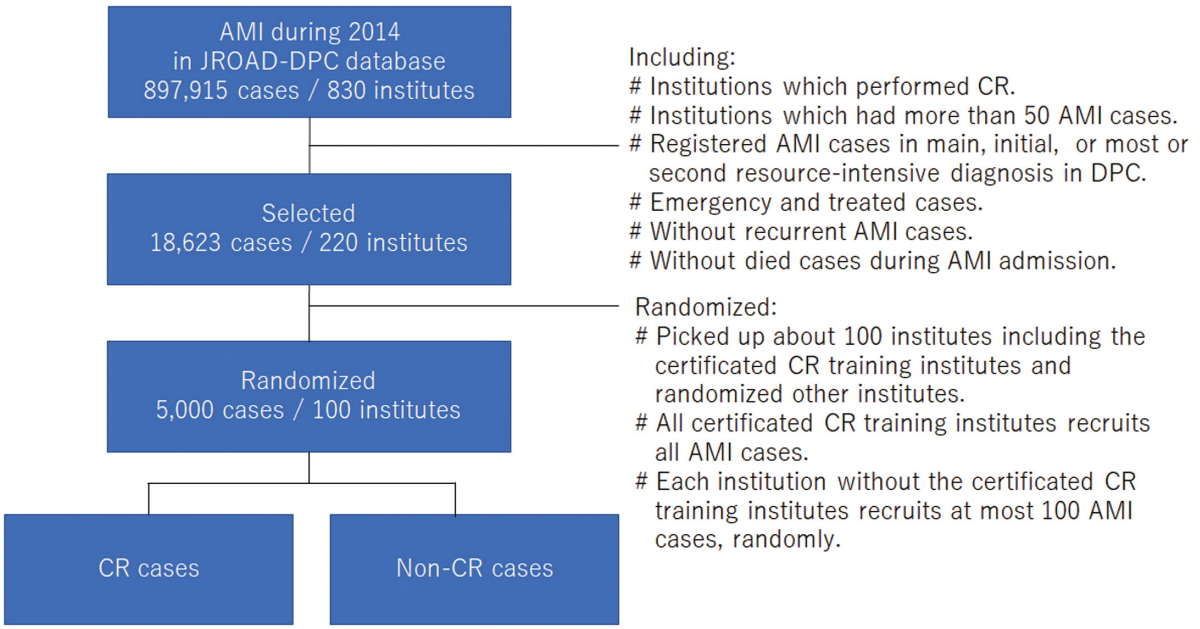
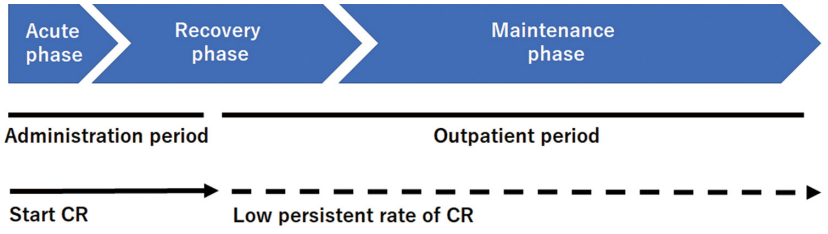


Figure 2. Study protocol. AMI, acute myocardial infarction; CR, cardiac rehabilitation; DPC, Diagnosis Procedure Combination; JROAD-DPC, The Japanese Registry of All cardiac and vascular Diseases Diagnosis Procedure Combination system.



Target
- Investigation about quality or quantity of CR
- The effectiveness of CR for cost
- The effectiveness of CR for prognosis
- Consideration for improving persistent rate of CR

Figure 3. Study concept. CR, cardiac rehabilitation.

that have not been certified for CR training, we will select those that had more than 50 cases of AMI in 2014. From each of the qualifying institutions that are not certified for CR training, we will randomly select up to 100 AMI patients (**Figure 2**). In addition, we expect to identify 1,950 patients who underwent CR among the 5,000 AMI patients. A previous meta-analysis reported that, among coronary artery disease (CAD) patients who did not receive CR treatment, the 3-year mortality rate due to cardiovascular disease was 14% and the 3-year MI recurrence rate was 13%.[7] Based on that study, we estimate that at least 32% of patients will show our primary endpoint. The introduction rate from hospitalization to outpatient rehabilitation is estimated to be 15%. Even if there are 15% of patients who are ineligible or lost to follow-up, it is possible to detect a relative risk (RR) reduction of ≥17.5% associated with inpatient and outpatient rehabilitation (i.e., RR ≤0.825, incidence rate ≤26.4% in the rehabilitation group) with 80% power (two-sided α=0.05). Patient recruitment will be both heterogeneous and representative, and the database will reflect the actual clinical situation in Japan.

Analysis Plan We will evaluate the associations of CR with prognosis and cost for AMI patients during admission and long-term follow-up (**Figure 3**). CR will be classified according to quantity and quality. We will also evaluate the start of the timing of CR, the risks of composite MACE, the percentage achievement for risk management, exercise tolerance, cardiac function, and the standards of the institution regarding CR, and analyze the associations of these factors with prognosis and cost. We will perform

subgroup analyses according to age, sex, underlying disease, AMI severity, cardiac function, and the presence of CR for outpatients. If necessary, we will perform propensity-score matching for survival analyses. We will make a prediction model for the prognosis and verify its validity.

Discussion

CR is a program for cardiovascular patients to improve their cardiovascular prognosis, quality of life, and activities of daily living. A previous meta-analysis in 2016 showed that CR was effective for reducing cardiovascular mortality (RR 0.74; 95% confidence interval [CI] 0.64–0.86) and the risk of hospital admission (RR 0.82; 95% CI 0.70–0.96) for CAD.[7] Cochrane reviews published in 2000[11] and 2011[12] also showed that CR for CAD was effective in reducing cardiovascular mortality and hospital admission. The effectiveness of CR for CAD must be evaluated for each era. We will also investigate the effectiveness of CR for all-cause death because this point remains controversial.

CR for CAD has been reported to reduce total cholesterol, triglyceride, systolic blood pressure, and smoking rate.[13] CR for CAD has also been shown to improve physical function.[14] Early CR for AMI patients (within 3 days) in the intensive care unit was safe and associated with reduced hospital cost and fewer days of hospital admission.[15] Based on this evidence, CR has a Class I recommendation for AMI during the acute, recovery, and maintenance phases. However, the participation rate in CR for AMI, and for outpatients in particular, remains low.[5] JROAD-CR will reveal the effectiveness of CR for AMI, and identify factors contributing to, and countermeasures against, the low CR participation rate in the era of early reperfusion therapy and shortened hospitalization.

Acknowledgments

The authors acknowledge the contributions made by participants of JROAD-CR in JROAD-CR registry facilities to manage the registry. The authors thank Japanese Association of Cardiac Rehabilitation (JACR) members for their support of this work.

Sources of Funding

This work was supported, in part, by funding from JACR and Fukuoka University (Grant no. 227302).

Disclosures

S. Miura has received remuneration from Otsuka Pharmaceutical Co., Ltd., Takeda Pharm. Co. Ltd., Daiichi Sankyo Co. Ltd., Bayer Yakuhin Ltd., and Boehringer-Ingelheim; research funding from Takeda Pharm. Co. Ltd., Daiichi Sankyo Co. Ltd., Abbott Medical Japan LLC, Boehringer-Ingelheim, Bayer Yakuhin Ltd., Astellas Pharma Inc., Sumitomo Dainippon Pharma. Co., Medtronic, HeartFlow Japan GK, MSD KK, Novartis, Pfizer Japan Inc., and TEIJIN Pharma; and scholarship funds from OMRON Co., SOMPO Japan, and Boston Scientific, Y. Suematsu has received research funding from Uehara Memorial Foundation and Suzuken Memorial Foundation. S. Miura, T.T., and Y.O. are members of *Circulation Reports*' Editorial Team.

IRB Information

The study protocol was approved by Fukuoka University Ethics Committee (No. U22-09-012) and the ethics committees of participating institutions.

Data Availability

The datasets will not be publicly available because patient consent in each institute does not allow for such publication. The corresponding author will respond to inquiries regarding data analyses.

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