Interventions supporting long term adherence and decreasing cardiovascular events after myocardial infarction (ISLAND): pragmatic randomised controlled trial

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WHAT IS ALREADY KNOWN ON THIS TOPIC
Secondary prevention treatments after myocardial infarction—namely, adherence to evidence based drug treatments and cardiac rehabilitation, are known to reduce morbidity and mortality
Many patients do not continue to take their cardiac drugs or complete cardiac rehabilitation after a myocardial infarction
Previous studies have suggested that educational reminders could help to improve long term adherence to secondary prevention treatments

WHAT THIS STUDY ADDS
A centralised, registry based intervention, informed by theory and a user centred design process, comprising mail-outs plus phone calls efficiently increased uptake of cardiac rehabilitation after a myocardial infarction but did not change adherence to medication

ABSTRACT
OBJECTIVE
To test a scalable health system intervention to improve long term adherence to secondary prevention treatments among patients who have had a recent myocardial infarction.

DESIGN
Three arm, pragmatic randomised controlled trial with blinded outcome assessment.

SETTING
Nine cardiac centres in Ontario, Canada.

PARTICIPANTS
2632 patients with obstructive coronary artery disease after a myocardial infarction, identified from a centralised cardiac registry.

INTERVENTIONS
Participants were randomised 1:1:1 to receive usual care, five mail-outs developed through a user centred design process, or mail-outs plus phone calls. The phone calls were delivered first by an interactive automated system to screen for non-adherence to treatment. Trained lay health workers followed up as necessary. Interventions were coordinated centrally but delivered from each patient’s hospital site.

MAIN OUTCOME MEASURES
Co-primary outcomes were completion of cardiac rehabilitation and adherence to recommended medication. Data were collected by blinded assessors through patient record and from administrative health databases at 12 months.

RESULTS
2632 patients (mean age 66, 71% male) were randomised: 878 to the full intervention (mail plus phone calls), 878 to mail only, and 876 to usual care. Of the respondents, 174 (27%) of 643 in the usual care group, 200 (32%) of 628 in the mail only group, and 196 (37%) of 531 allocated to the full intervention completed cardiac rehabilitation (adjusted odds ratio 1.55, 95% confidence interval 1.18 to 2.03). In the mail plus phone group, 11.7%, 6.0%, 14.4%, 32.9%, and 35.0% reported adherence to 0, 1, 2, 3, and 4 drug classes after one year, respectively, in comparison with 12.5%, 6.8%, 13.6%, 30.2%, and 36.8% in the mail only group, and 12.2%, 8.4%, 13.1%, 30.3%, and 36.1% in the usual care group, respectively (mail only v usual care, odds ratio 0.98, 95% confidence interval 0.81 to 1.19; full intervention v usual care, 0.99, 0.82 to 1.20).

CONCLUSIONS
Scalable interventions delivered by mail plus phone can increase completion of cardiac rehabilitation after myocardial infarction but not adherence to medication. More intensive interventions should be tested to improve adherence to medication and to evaluate the association between attendance at cardiac rehabilitation and adherence to medication.

TRIAL REGISTRATION
ClinicalTrials.gov NCT02382731, registered 9 March 2015 before any patient enrolment.

Introduction
For nearly all patients after a myocardial infarction, with evidence of coronary artery disease, guidelines recommend long term use of four classes of drugs: statins, antiplatelets, β blockers, and angiotensin system inhibitors (that is, angiotensin converting enzyme inhibitors or angiotensin receptor blockers). The drugs seem to have an additive effect, such that adherence to more of them is associated with lower mortality, lower morbidity, and lower costs to the health system.1 2 After a myocardial infarction, most patients are discharged with these drugs. Suboptimal adherence to cardiac drugs is common, however, and around half of patients discontinue their medication by 12 months after myocardial infarction.3 4 In addition to drugs, guidelines for secondary prevention of myocardial infarction recommend participation in cardiac rehabilitation. Patients are given information to enhance control of risk factors and adherence to cardiac drugs and provided with a supervised plan for physical activity, either in a healthcare institution or at home, to reduce cardiovascular mortality and
improve quality of life. Unfortunately, most patients are not referred to—and hence do not participate in—cardiac rehabilitation programming after myocardial infarction.

The 2014 Cochrane review of interventions to enhance adherence to medication noted that many trials feature multifaceted interventions that would be expensive to implement at scale. Conversely, a recent economic analysis indicated that all of the strategies available to improve adherence to drug treatment after myocardial infarction, educational reminders sent by mail are the most likely to be cost effective. The 2019 Cochrane review of interventions to enhance adherence to rehabilitation identified relatively low cost interventions, including mailed letters, as successful if tailored to the patient’s barriers, but concluded that further trials were needed to inform best practice.

Here, we present the results of the Interventions Supporting Long term Adherence aNd Decreasing cardiovascular events after myocardial infarction (ISLAND) trial. ISLAND tested the effects of a series of mailed educational reminders, with or without the addition of phone calls from an automated interactive voice response system and a trained lay health worker, compared with usual care for adherence to recommended secondary prevention treatments.

**Methods**

**Study design**

ISLAND was a pragmatic, multicentre randomised controlled trial with blinded assessment of outcome to evaluate interventions designed to improve long term adherence to recommended secondary prevention treatment after myocardial infarction. To maximise efficiency, the approach involved automated enrolment from an existing provincial registry, centralised delivery of the intervention, and use of routinely collected administrative data. Embedded within the trial was a process evaluation, which is reported separately. The study was funded by the government of Ontario through open, peer reviewed competition; the funder did not participate in the methods, analysis, interpretation, or dissemination of the results. Methodological details of both the trial and the process evaluation have been described previously.

The trial was approved by nine research ethics boards, facilitated by Clinical Trials Ontario (project ID 0720), and the protocol is registered on clinicaltrials.gov (NCT02382731).

**Setting**

In Ontario, Canada, co-payments for visits to physicians or to hospital based cardiac rehabilitation programmes are not required. Prescription drugs are covered for patients aged 65 and older, but younger patients pay out-of-pocket or through private insurance plans, unless they qualify for social support. CorHealth Ontario (https://www.corhealthontario.ca/) is an agency funded by the government of Ontario to improve cardiac, stroke, and vascular care in the province. For every cardiac catheterisation in Ontario, a standardised case report form is completed and provided to the CorHealth Cardiac Registry by the cardiac centre; aggregated and de-identified data are routinely used for health system planning.

**Participants**

Nine of 18 cardiac care centres in the province participated in this study. Convenience sampling (that is, networking by the study team) was used to recruit participating centres, with representation from both community and academic settings, and from those with and without cardiac surgical back up, to maximise the generalisability of the findings and the potential for scalability. Patients were considered eligible if they were adults with a valid provincial health card number, had a coronary angiogram after a myocardial infarction (ST elevation myocardial infarction or non-ST elevation myocardial infarction) with evidence of obstructive coronary artery disease (based on visual assessment of the coronary angiogram, defined as >50% luminal stenosis of the left main artery or >70% luminal stenosis of one or more major epicardial coronary arteries), and were discharged alive from the cardiac centre after the procedure. We excluded those patients with cardiogenic shock (Killip class 4) at the time of their angiography, owing to poor prognosis. We also excluded patients who required a translator to receive services in English (because it was not feasible to offer the interventions in many languages) and those with incomplete registry data by one month after angiography (because they could not receive the intervention as intended). All eligible patients at participating centres, as assessed using routinely collected data, were enrolled. The research ethics boards approved the study, with a waiver of patient informed consent; participants were provided with pertinent information, with the option to opt out at all contact points.

**Allocation**

Using a predefined algorithm, CorHealth searched its cardiac registry each week for eligible patients and provided the resulting list to each participating cardiac centre. Each centre then forwarded the list to the trial coordinating centre (Population Health Research Institute, McMaster University, Hamilton, Ontario) to act on their behalf. From September 2015 through May 2016, participants were assigned a unique study identifier and allocated 1:1:1 to the three trial arms, stratified by cardiac centre, after randomisation generated by an independent statistician using a permuted block design with randomly varying block sizes. Randomisation was performed using an automated centralised software platform at the Population Health Research Institute. In accordance with the standard operating procedures of the research institute, designated unblinded statisticians (independent of the conduct of the study) prepared and validated the randomisation schedule. The schedule was then securely transferred to the
developers at the information and communications technology department, who incorporated it into the randomisation system. Access to randomisation schedules was strictly controlled, with no admission by unauthorised staff, including researchers, study team members, and site staff.

**Interventions**

Interventions were developed to be scalable and sustainable for implementation across health systems, and were systematically developed and informed by behavioural science, patient input,\(^\text{17}\) a user-centred design process,\(^\text{18}\) and results of a pilot trial.\(^\text{9}\) Interventions were coordinated and performed centrally but delivered on behalf of the cardiology team at the hospital where the patient had their index coronary angiogram. Interventions were timed to correspond with the likely need for prescription refills, because we have previously shown that these are vulnerable times for adherence to medication.\(^\text{8}\)

Interventions with varying, tailored content were delivered by mail and by telephone about 4, 8, 20, 32, and 44 weeks after myocardial infarction.

**Mail-out reminders**

A series of mailed booklets—developed in partnership with a design firm (https://pivot.design/), a lead patient partner, and patients and family members who had survived a myocardial infarction—encouraged participation in rehabilitation and long-term adherence to cardiac drugs. The booklets included prompts to develop action plans focusing on discussion of concerns about treatment with providers; obtaining drug refills; daily adherence to medication; and participation in rehabilitation.\(^\text{19}\) The first two booklets enclosed a letter for the patient to take to their doctor. This letter provided evidence in support of rehabilitation and persistence with cardiac drugs, suggestions for improving adherence, and a prefilled referral form with details of local cardiac rehabilitation programmes (to deal with the barrier of non-referral to rehabilitation at discharge). A description of the design process along with samples of the mail-outs has been previously published.\(^\text{18}\)

**Mail-out reminders plus telephone calls**

Phone calls were made by an automated interactive voice response system one to two weeks after each mail-out. This system, delivered by a third party firm (https://www.vocantas.com), responds to verbal or push button answers and provides further content accordingly based on a structured algorithm (see sample in appendix). Patients reporting non-persistence with their drugs or rehabilitation and those who reported they had not seen their healthcare team in the previous three months were encouraged by the system to discuss solutions with their healthcare providers. These patients, and those who reported they did not receive the letter and who could not be contacted by the automated system, received phone calls by a trained lay health worker. Not all lay health workers had a history of myocardial infarction because recruitment was difficult. These health workers were trained to identify barriers to adherence that could be modified and provide tailored advice according to structured scripts. Training involved teaching by a cardiac care nurse in person, adapting an existing lay health worker curriculum\(^\text{20}\) that covers basic pathophysiology and the role of medication and rehabilitation. Lay health workers received readings on these topics and took part in role play with the telephone scripts and data collection forms, followed by supervised study phone calls, until they were competent to make independent calls. The telephone scripts dealt with common topics—for example, encouragement of patients to make appointments with their healthcare team, strategies to remember to take their drugs, and making action plans for rehabilitation. The scripts did not provide clinical advice and directed patients to seek medical advice, as appropriate (see sample in appendix).

**Usual care**

No attempt was made to standardise care.\(^\text{21}\) Usual care in Ontario includes communication between the hospital team, the primary care provider, and when relevant, the outpatient specialist (internist or cardiologist). The quality of such communication or discharge summaries varies widely even within the same institution. Summaries often lack necessary recommendations for long-term treatment.\(^\text{22}\)

**Data collection**

Study data were obtained from two sources—namely, patient self-report and administrative data. Patient reported data were collected explicitly for this trial through telephone calls by blinded research staff with study participants at 12 months from baseline. During these calls, the adherence of participants to secondary prevention treatments after myocardial infarction was assessed. We used a previously validated approach to ask patients about the percentage of prescribed cardiac rehabilitation sessions (whether for education or exercise) attended and whether they completed the rehabilitation programme.\(^\text{23}\) Active cardiac drugs at the time of outcome assessment were identified by open-ended questions—for example, “list your current prescription medications”). An adapted version of the Brief Medication Questionnaire was used to inquire about missed pills (that is, days missed in the past seven days and past 30 days, respectively) for active cardiac drugs, using an approach previously validated for statins against cholesterol levels\(^\text{24}\) and for non-adherence to antihypertensive treatment against pill counts and pharmacy records.\(^\text{25}\) Additionally, disease-specific quality of life was assessed using the Seattle Angina Questionnaire\(^\text{7,26}\) and sociodemographic information (for example, smoking status, marital status, highest level of education attained, ethnicity, and insurance coverage for medication) was collected.

Routinely collected administrative data were also extracted for recruitment and analysis. Patients were
identified from the CorHealth Cardiac Registry, which contains basic sociodemographic information on patients undergoing cardiac tests and procedures, such as angiography, in addition to the subsequent findings. These baseline data from CorHealth were first linked with the ISLAND database, which contained patient reported responses to trial questionnaires. The data were then linked with other health administrative databases held at ICES through a unique identifier based on provincial health card numbers of the participants. ICES is an independent, non-profit research institute legally allowed to collect and analyse healthcare and demographic data, without consent, for evaluation and improvement of the health system. At ICES, administrative datasets related to drugs, healthcare use, vital status, and more were linked using unique encoded identifiers for analysis.

Outcomes
As noted in the published protocol, after extensive interaction with stakeholders involved in the project, we defined two co-primary outcomes, which were assessed 12 months after myocardial infarction through patient self-report. Firstly, adherence to recommended classes of cardiac drugs (statins, antiplatelets, β blockers, and angiotensin system inhibitors), measured on an ordinal scale (range 0-4), where 0 represents tablets missed in the past seven days for any of the recommended classes of drug, and 4 represents no missed tablets in the past seven days for each recommended class of drug and 4 represents no missed tablets in the past seven days for each recommended class of drug.24 25 27 If patients identified multiple persistent cardiac drugs within the same class, the drug with the lowest reported frequency of days missed in the past seven days was used to define adherence for that specific class. Secondly, completion of rehabilitation, because programme completion/graduation has been associated with greater risk reduction28 than partial or no attendance.

Secondary outcomes were also assessed at 12 months, using either patient reported data or provincial administrative claims data (according to the full definitions described in the published protocol). Secondary outcomes based on patient reported data included health related quality of life (based on response to the Seattle Angina Questionnaire-7), smoking status (any cigarette smoking in the past three months), enrolment for rehabilitation (attended at least one session), rehabilitation attendance (proportion of prescribed sessions attended), and adherence (and persistence) for each class of drug. As there is no consensus on best practice to assess patient reported adherence to medication, alternative measures were specified a priori as secondary outcomes. Patient reported adherence to medication was also assessed using days missed in the past 30 days (less than six days missed was deemed adherent). Adherence to all recommended classes of cardiac drugs was assessed29 as a dichotomous outcome. Lastly, adherence to dual antiplatelet treatment was defined as adherence to aspirin and a secondary antiplatelet (that is, clopidogrel, prasugrel, or ticagrelor).30

Secondary outcomes derived from administrative data sources included healthcare use (eg, number of visits to the emergency department, hospital admissions, outpatient assessments), mortality, and occurrence of cardiovascular events (hospital admissions for myocardial infarction or cardiac interventions). Additionally, for those participants over 65—that is, those who would be guaranteed coverage by the Ontario drug benefit programme due to age—adherence to medication was assessed using administrative data. Owing to poor capture of aspirin in Ontario administrative data, which does not obtain details of over-the-counter dispensations, adherence to antiplatelets through administrative data was measured excluding aspirin. In contrast to the published protocol, adherence to medication, as defined by administrative claims, was measured using the mean proportion of days covered in the past 365 days for three recommended classes of drug, and the proportion of days covered for each individual class, because this is more conservative than mean possession ratio.31

Statistical analysis
All analyses adhered to modified intention-to-treat principles, whereby a subset of all randomised participants was analysed. The approach deviated from a true intention-to-treat approach in that randomised participants who were truly ineligible or were unable to receive any intervention (irrespective of allocation) were excluded. Owing to the pragmatic nature of our recruitment process, where eligibility and baseline data were both obtained through the CorHealth Cardiac Registry, we expected that a small number of randomised participants would later be deemed ineligible because of misclassification errors in the administrative data. Consequently, patients who reported never having had an acute myocardial infarction at their first point of contact (after baseline), which was later confirmed by a study cardiologist, were excluded on these grounds. Secondly, we excluded patients who died within 27 days after baseline, because these patients were never able to receive an intervention. The proportion of participants excluded after randomisation was compared among treatment groups by a test for equality of proportions.

Primary outcome analyses
To assess the effect of each intervention arm on completion of cardiac rehabilitation (dichotomous outcome), we performed binary logistic regression. We used ordinal logistic regression with a cumulative logit link function to evaluate the effect of each intervention in comparison with usual care on the number of classes of cardiac drugs to which patients adhere. We used the score test to assess the proportional odds assumption. For each primary outcome regression analysis, an odds ratio with corresponding 95% confidence interval was estimated for each comparison of an intervention with usual care. Each analysis adjusted for the stratification factor in randomisation (centre) using a
fixed covariate. To account for multiple comparisons arising from contrasting two interventions with usual care for two primary outcomes, we applied the step-down Šidák procedure for post-hoc adjustment of the P value to maintain a family-wise type I error rate of 5% across all four comparisons. To complement the logistic regression results for rehabilitation completion, the effect of each intervention arm was also summarised as an absolute risk difference through binomial regression with an identity link.

The protocol planned for a sample size of 914 patients in each arm, for an overall total of 2742 patients. This calculation was based on detecting a minimally important difference in at least one of the co-primary outcomes with minimum 80% power, accounting for multiple testing across two outcomes and a three arm design, maintaining the overall α level at 5% using the step-down Šidák procedure.

For completion of cardiac rehabilitation, a control arm proportion of 35% was assumed and a minimally important difference of 9% was specified. For adherence to medication, it was assumed that 3%, 12%, 35%, and 50% of participants in the control arm would respectively be adherent to one or fewer, two, three, or four recommended classes of drug (based on data from the pilot study), with a minimally important odds ratio of 1.45 specified. With these assumptions, it was estimated that 685 analysable patients in each group were required for the rehabilitation outcome using a χ² test, and 635 in each group for adherence to medication using Whitehead’s method for ordinal outcomes. We inflated this by 25% to account for expected loss to follow-up.

Sensitivity analyses
Multiple sensitivity analyses were performed to test the robustness of our findings to specific methodological and clinical decisions. We repeated the primary regression analyses after independently excluding those who died within 28 to 365 days after randomisation; secondly, specifying centre as a random effect; thirdly, assuming those who were not reached were non-adherent; and lastly, excluding those who refused to complete an outcome assessment. For adherence to medication, we recoded response values for patients with less clear indications for a β blocker (defined as a history of asthma or left ventricular ejection fraction >40%) or angiotensin inhibitor (defined as having a history of end stage renal disease, left ventricular ejection fraction >40%, diabetes, or hypertension). Patients’ ordinal scores for adherence to medication were increased by a value of one (towards the upper limit of four) for each class of drug for which they had a less clear indication.

Subgroup analyses
Potential effect modification by patient sociodemographic characteristics (that is, age group ≥65 v <65), sex, smoking history, neighbourhood income quintile, or rurality) and clinical characteristics (that is, diabetes status, prior cardiac event, or revascularisation) was independently explored by including a fixed effect for each characteristic and statistical interaction terms between that characteristic and each intervention to the primary regression analyses.

Analysis of secondary outcomes
To assess the effect of each intervention on dichotomous and ordinal secondary outcomes, respectively, binary and ordinal logistic regressions were conducted. Treatment effects for count based outcomes (that is, healthcare use measures) were estimated using negative binomial regression, and for continuous outcomes using linear regression. Regression models for dichotomous, ordinal, count based, and continuous secondary outcomes included fixed effects for treatment group and centre. To evaluate differences in time-to-event outcomes (that is, death), we produced Kaplan-Meier curves for each treatment group and compared survival by a stratified log rank test (centre as stratifying factor). To estimate the effect of each intervention on patient survival, hazard ratios were estimated with corresponding 95% confidence intervals by stratified Cox proportional hazards regression (centre as stratifying factor). All survival analyses were conducted using administrative data on mortality, which enabled follow-up of patients at 365 days, irrespective of whether they responded to the ISLAND questionnaire.

Handling of missing data
Consistent with the published protocol, the primary analysis treated individuals who died within 28 days to 365 days after randomisation as non-adherent to both primary outcomes. For patients who opted out, did not respond (no contact), or refused to complete an outcome assessment at 12 months, we used multiple imputation as for all patient reported outcomes under an assumption of missing at random. With this assumption, the reasons for withdrawal, non-response, or refusal were considered to be unrelated to the outcomes but fully explained by a set of observed variables. In particular, for both primary outcomes, centre, treatment group, and all characteristics involved in planned subgroup analyses were included in their respective multiple imputation models. In addition, auxiliary information was included in the multiple imputation model to make the assumption of missing at random more tenable. For each patient reported outcome with missing responses, auxiliary variables were identified as those correlated with the observed value (as assessed by a Pearson correlation coefficient of ≥0.4) or “missingness” (by logistic regression) for that outcome. We imputed 20 datasets using fully conditional specification, which allowed a unique imputation model to be specified for each outcome. Multiple imputation offered several advantages over complete case analysis because it maximised the use of all available data, including baseline characteristics for the participants lost to follow-up; it allowed us to reduce the potential bias due to differences in
outcomes between participants who were lost to follow-up and those with complete data; and finally, it accounted for the uncertainty associated with the imputed values. The multiple imputation process is fully summarised in the statistical appendix. Finally, we tested sensitivity to an assumption of missing not at random by using single imputation under extreme assumptions about the missing data. All statistical analyses were performed in SAS version 9.4, with statistical significance assessed by a two tailed P value ≤0.05.

Patient and public involvement
In this project, we involved patients at the outset to solicit input about the intervention content. The lead patient partner helped to gather input from additional patients and worked with the design team to iteratively develop the intervention materials, following user centred design methodology. This process was described in detail in a previous manuscript.18 Briefly, the process involved meeting a series of patients who experienced a heart attack to develop the content of the materials and was facilitated by a professional, user experience, design group.

Given the waiver of consent, it was important to solicit input about the potential burden of the intervention and to adjust the design accordingly. We plan a lay summary of the results and implications, which will be disseminated through partnerships with relevant organisations.

Results
Recruitment and follow-up of study population
eFigure 1 shows details of the construction of the final study population, which consisted of 2632 participants after excluding 110 (4.0%) of the 2742 randomised patients who were either truly ineligible to participate (that is, reported having no myocardial infarction, which was later validated by a cardiologist on the study team) or died within 27 days (inclusive) of randomisation, and thus were unable to receive an intervention. The proportions of participants removed by the exclusions after randomisation did not differ among the three treatment groups (usual care, n=36 or 3.9%; mail-outs, n=37 or 4.0%; mail-outs plus phone calls, n=37 or 4.0%; χ²(2)=0.15, P=0.99).

Loss to follow-up was higher than expected and varied across the experimental arms (eFigure 1). A greater proportion of patients who refused an outcome assessment at 12 months belonged to the mail plus phone group (231 (72.4%) of 319 refusals; χ²(2)=247, P<0.001). Additionally, those who refused were about three years older, on average, than those who did not refuse (mean difference, 3.13 (standard deviation 0.73), 95% confidence interval −4.57 to −1.70; P<0.001; supplemental table 1).

We categorised those who actively refused separately from those who passively did not respond. Among those who did not die during follow-up, 75 patients asked to discontinue their allocated intervention (eFigure 1). Seventy four of these patients (98.7%) were allocated to the mail plus phone calls group, of whom almost all refused any further phone calls (72 or 97.3%; automated interactive voice response or non-automated) with 19 (25.7%) solely refusing automated calls.

Among 878 participants in the primary analysis for the mail plus phone group, a total of 9537 automated calls were attempted during the trial. Of these 9537 calls, 4650 (48.8%) were answered by someone and 453 (4.7%) were made to an invalid number. In total, 1914 (41.2%) of all answered interactive voice response calls were completed; at the patient level, these 1914 successful automated calls were made to 622 (70.8%) of 878 participants. During the trial, an average of 3.08 (standard deviation 1.44) completed automatic calls were made to each participant in the mail plus phone group (maximum according to protocol=5). In accordance with the protocol, patients with an incomplete interactive voice response call and those with a “flag” on their automatic call received a phone call from a lay health worker. Overall, 654 (74.5%) of 878 patients in the mail plus phone arm completed a phone call from a lay health worker. On average, participants in the mail plus phone group completed 2.03 (standard deviation 1.71) calls from lay health workers during follow-up (maximum according to protocol=5).

Patient characteristics
Table 1 summarises baseline patient characteristics by treatment group. The three trial arms were well balanced; patients were primarily male (71.3%) and older adults (mean age 66.0; standard deviation 12.4). Overall, 972 (36.9%) of 2632 patients reported a previous cardiac event or cardiac procedure at baseline. Our exclusions after randomisation did not induce statistically significant imbalances at baseline among the three groups for any of the characteristics summarised in table 1.

Effect of interventions on cardiac rehabilitation completion, and adherence to medication
Of the 2632 patients in our primary analysis, 1802 (68.5%) and 1603 (60.9%) provided a response to the completion of cardiac rehabilitation and adherence to medication co-primary outcomes, respectively (table 2). Of respondents, 174 (27%) of 643 in the usual care group, 200 (32%) of 628 in the mail only group, and 196 (37%) of 531 in the mail plus phone group completed cardiac rehabilitation. Adherence to all four classes of cardiac drugs was reported by 207 (36%) of 574 in the usual care group, 200 (37%) of 543 in the mail-out only group, and 170 (35%) of 486 in the mail plus phone group. The distribution of observed responses for each primary and secondary outcome by group—both before and after imputation—is available in supplemental table 2.

Table 3 summarises regression results for the co-primary outcomes. Neither intervention resulted in significant changes to adherence to medication.
Patients in the mail plus phone group showed greater odds of completing cardiac rehabilitation than usual care (odds ratio 1.55, 95% confidence interval 1.18 to 2.03). On the absolute scale, more patients in the mail plus phone group completed cardiac rehabilitation than patients in the usual care group (adjusted risk difference 9.4%, 95% confidence interval 3.5% to 15.4%). Patients in the mail only group had a non-statistically significant increase in cardiac rehabilitation completion (adjusted risk difference 3.7%, 95% confidence interval −1.0% to 8.4%).

None of the planned sensitivity analyses meaningfully altered our results. Relaxing the proportional odds assumption for treatment group when modelling adherence to medication did not substantially alter our findings (supplemental table 3). Exploratory analyses indicated that effects of mail only and mail plus phone calls on either co-primary outcome did not differ across selected demographics (eg, age, sex) and clinical subgroups (that is, diabetes status, prior cardiac event or procedure; supplemental table 4).

Table 1 | Patient characteristics by treatment group at baseline among 2632 patients after myocardial infarction. Values are number (%) unless stated otherwise

| Characteristics                          | Usual care (n=876) | Mail-outs (n=878) | Mail-outs and phone calls (n=878) | Total (n=2632) |
|-----------------------------------------|-------------------|------------------|-----------------------------------|---------------|
| Centre:                                 |                   |                  |                                   |               |
| A                                       | 175 (20.0)        | 180 (20.5)       | 172 (19.6)                        | 527 (20.0)    |
| B                                       | 61 (7.0)          | 62 (7.1)         | 62 (7.1)                          | 185 (7.0)     |
| C                                       | 130 (14.8)        | 131 (14.9)       | 129 (14.7)                        | 390 (14.8)    |
| D                                       | 78 (8.9)          | 72 (8.2)         | 76 (8.7)                          | 226 (8.6)     |
| E                                       | 75 (8.6)          | 71 (8.1)         | 73 (8.3)                          | 219 (8.3)     |
| F                                       | 111 (12.7)        | 116 (13.2)       | 14 (1.6)                          | 341 (13.0)    |
| G                                       | 54 (6.2)          | 55 (6.3)         | 55 (6.3)                          | 164 (6.2)     |
| H                                       | 58 (6.6)          | 56 (6.4)         | 62 (7.1)                          | 176 (6.7)     |
| I                                       | 134 (15.3)        | 135 (15.4)       | 135 (15.4)                        | 404 (15.3)    |
| Age, mean (SD)                          | 66.8 (12.5)       | 66.8 (12.6)      | 65.9 (12.1)                       | 66.0 (12.4)   |
| Ontario Drug Benefit Programme coverage due to age ≥65: |                   |                  |                                   |               |
| No                                      | 402 (45.9)        | 392 (44.6)       | 436 (48.5)                        | 1230 (46.4)   |
| Yes                                     | 474 (54.1)        | 486 (55.4)       | 452 (51.5)                        | 1412 (53.6)   |
| Sex:                                    |                   |                  |                                   |               |
| Male                                    | 624 (71.2)        | 626 (71.3)       | 626 (71.3)                        | 1876 (71.3)   |
| Female                                  | 252 (28.8)        | 252 (28.7)       | 252 (28.7)                        | 756 (28.7)    |
| Rurality:                               |                   |                  |                                   |               |
| Rural                                   | 141 (16.1)        | 153 (17.4)       | 132 (15.0)                        | 426 (16.2)    |
| Urban                                   | 731 (83.4)        | 719 (81.9)       | 741 (84.4)                        | 2191 (83.2)   |
| Missing                                 | 4 (0.5)           | 6 (0.7)          | 5 (0.6)                           | 15 (0.6)      |
| Neighbourhood income (divided into five equal groups)*: |                   |                  |                                   |               |
| 1 (lowest)                              | 186 (21.2)        | 184 (21.0)       | 195 (22.2)                        | 565 (21.5)    |
| 2                                       | 196 (22.4)        | 188 (21.4)       | 182 (20.7)                        | 566 (21.5)    |
| 3                                       | 171 (19.5)        | 170 (19.4)       | 165 (18.8)                        | 506 (19.2)    |
| 4                                       | 159 (18.2)        | 168 (19.1)       | 189 (21.5)                        | 516 (19.6)    |
| 5 (highest)                             | 160 (18.3)        | 162 (18.5)       | 142 (16.2)                        | 464 (17.6)    |
| Missing                                 | 4 (0.5)           | 6 (0.7)          | 5 (0.6)                           | 15 (0.6)      |
| Previous cardiac event or procedure†:   |                   |                  |                                   |               |
| No                                      | 512 (58.4)        | 523 (59.6)       | 535 (60.9)                        | 1570 (59.7)   |
| Yes                                     | 333 (38.0)        | 319 (36.3)       | 320 (36.4)                        | 972 (36.9)    |
| Missing                                 | 31 (3.5)          | 36 (4.1)         | 23 (2.6)                          | 90 (3.4)      |
| History of smoking:                     |                   |                  |                                   |               |
| Never                                   | 326 (37.2)        | 320 (36.4)       | 338 (38.5)                        | 984 (37.4)    |
| Current                                 | 214 (24.4)        | 209 (23.8)       | 207 (23.6)                        | 630 (23.9)    |
| Former                                  | 239 (27.3)        | 232 (26.4)       | 242 (27.6)                        | 713 (27.1)    |
| Missing                                 | 97 (11.1)         | 117 (13.3)       | 91 (10.4)                         | 305 (11.6)    |
| Diabetes:                               |                   |                  |                                   |               |
| No                                      | 591 (67.5)        | 599 (68.2)       | 594 (67.7)                        | 1784 (67.8)   |
| Yes                                     | 277 (31.6)        | 267 (30.4)       | 275 (31.3)                        | 819 (31.1)    |
| Missing                                 | 8 (0.9)           | 12 (1.4)         | 9 (1.0)                           | 29 (1.1)      |
| Treatment at index catheterisation:     |                   |                  |                                   |               |
| Surgery and medication                  | 26 (3.0)          | 20 (2.3)         | 22 (2.5)                          | 68 (2.6)      |
| Stent and medication                    | 529 (60.4)        | 552 (62.9)       | 532 (60.6)                        | 1613 (61.3)   |
| Medication only                         | 321 (36.6)        | 306 (34.9)       | 326 (36.9)                        | 951 (36.1)    |

Owing to rounding, the sum of column percentages might exceed 100%. The variables included represent a subset of those collected by the investigators from the CorHealth registry. This subset was chosen as all the variables in table 1 were adjusted for in at least one multiple imputation model (supplementary statistical appendix). No significant differences in any measured baseline characteristics were found among treatment groups at P≤0.05. *Derived on the basis of participant’s postal code using a macro created by Statistics Canada. †Indicator representing whether a patient had a history of prior myocardial infarction coronary vascular disease, or coronary revascularisation (percutaneous coronary intervention or coronary artery bypass graft) procedure.
Effect of interventions on secondary outcomes

Table 6 summarises the secondary outcomes. Enrolment for, and attendance at, cardiac rehabilitation increased in both intervention groups compared with usual care, but the relative treatment effects were larger for the mail plus phone intervention. No statistically significant differences were noted between groups for outcomes showing adherence or persistence to medication, whether measured by patient report or administrative data. In particular, no differences across groups were seen for adherence to medication assessed with administrative data in patients over age 65, for whom the costs of medication would not be a problem. More patients in the mail-out only group compared with usual care attended an emergency department in the year after myocardial infarction. No other differences between groups were noted for outpatient visits, hospital admissions, or repeat cardiovascular events.

As shown in eFigure 1, a total of 130 patient deaths were recorded during ISLAND follow-up by research staff among 2632 patients. In contrast, 137 patient deaths (that is, an additional seven) were identified using administrative data among 2624 patients (eight could not be linked to administrative claims). Despite this small difference, the two data sources were highly concordant in classifying patient mortality status ($\kappa$ coefficient 0.93, 95% confidence interval 0.90 to 0.96) with the proportion of deaths identified from each source found to be statistically equivalent according to McNemar’s test ($\chi^2(1)=2.88; P=0.09$).

Of the 137 deaths identified through administrative claims, 52 (38.0%), 50 (36.5%), and 35 (25.5%) occurred among the usual care, mail only, and mail plus phone calls groups, respectively. eFigure 2 compares survival between 28 and 365 days after randomisation by allocated treatment group using administrative claims data. The Kaplan-Meier curve corresponding to the mail plus phone calls group seems to separate from the other two treatment groups around 180 days; however, the difference in survival was not statistically significant among the three treatment groups according to a stratified log rank test ($\chi^2(2)=4.01; P=0.13$). Based on a Cox proportional hazards regression model on 2624 patients, neither mail-outs (hazards ratio 0.98; 95% confidence interval 0.67 to 1.45) nor mail-outs plus phone calls (0.67, 0.43 to 1.03) had a statistically significant effect on the hazard of death in comparison with usual care.

Discussion

Principal findings

In this pragmatic trial, we used existing data to identify eligible patients, to coordinate the delivery of patient centred, scalable interventions informed by behavioural theory, and to enable follow-up of patients from nine community and academic cardiac centres. The measured adherence to medication and completion of rehabilitation were both lower than expected. Under usual care at 12 months after myocardial infarction, only 174 (27%) of 643 participants completed cardiac rehabilitation and 207 (36%) of 574 were fully adherent to all recommended classes of cardiac drug, showing the need for interventions like the ones tested in this trial. The provision of mail-outs plus phone calls was associated with significantly greater odds of fully completing cardiac rehabilitation compared with usual care (odds ratio 1.55, 95% confidence interval 1.18 to 2.03) but did not alter adherence to medication. These findings were robust to a number of sensitivity analyses and consistent across subgroups.

Comparison with previous evidence

For cardiac rehabilitation enrolment, adherence, and completion we observed a graded intervention effect, with mail-outs alone increasing enrolment compared with usual care slightly less than the full intervention with mail plus phone calls. The results for the outcome examining the proportion of cardiac rehabilitation sessions attended were similar. These results align with prior evidence from smaller trials, suggesting that mail-outs with theory informed content encourage rehabilitation attendance. The effect sizes obtained fit well with the findings of the Cochrane systematic review on increasing uptake of cardiac rehabilitation.14 Although our interventions were personalised, the centralised and pragmatic approach used in this study did not allow for tailoring by age or sex, and this could represent an opportunity for future research.37 38
Evidence for interventions with an interactive voice response system is still emerging, and effects probably depend on the specific content of the messages provided. Previous evidence suggests that this automatic system could cost effectively improve adherence to cardiac drugs. We adapted the successful approach used in one (non-participating) hospital in Ontario combining an interactive voice response system and nurse telephone case managers by moving tasks to trained lay health workers. Our intention was that lay health workers could help those patients identified by the automatic voice response system to overcome barriers to treatment goals. The finding that the mail-out alone group made more visits to the emergency department but that mail plus phone group was similar to control could be spurious but raises the possibility that the phone based interventions could have provided useful responses to concerns raised by the written materials. Possibly, the types of barriers to rehabilitation encountered by participants are more amenable to non-clinical support from lay health workers than those related to medication. Additionally, it could be that the content of the interventions did not deal effectively with the role of medication in recovery or that the booklets did not adequately draw attention of recipients to the actions they needed to take to adhere to long term medication. Improving adherence to medication may require more intensive interventions and perhaps, clinically trained staff, to deal with misinformed beliefs or concerns about possible adverse effects.

Strengths and limitations
The trial followed a highly pragmatic approach to testing a system-wide initiative. Research ethics boards at each of the nine cardiac centres approved the waiver of consent, in view of the need for rigorous evaluation of the intervention and the limited perceived burden or risk of the interventions. Without randomised evaluation, incorrect conclusions could have been reached in this trial. Embedding multimodal, pragmatic trials of interventions aiming at implementing improved care or outcomes within routine operations of health systems can help to reduce research waste in implementation science by producing generalisable scientific results, and findings that directly improve patient care. Our partnership with CorHealth was essential for this study and shows the potential of this learning health system approach for improving health system performance.

We acknowledge limitations in this trial including patient self-reporting of the primary outcomes. The questions used to assess rehabilitation were previously validated against programme audits in Ontario. The administrative database analysis offers partial validation for the assessment of adherence to medication. The consistency of results across measures of adherence to, and persistence with, medication also offers reassurance about validity. Data were not available for prescriptions provided to patients.

Table 4 | Secondary outcome regression results using both patient-reported and administrative claims data at 12 months after myocardial infarction. Values are odds ratio (95% confidence interval)

| Source, outcome, and intervention* | Effect estimate (95% CI) | P value |
|------------------------------------|--------------------------|---------|
| **Patient-reported (n=2502)**      |                          |         |
| Cardiac rehabilitation enrolment (yes/no): |                          |         |
| Mail-outs (n=829) | 1.27 (1.01 to 1.61) | 0.05 |
| Mail-outs plus phone calls (n=844) | 1.55 (1.23 to 1.95) | <0.001 |
| Cardiac rehabilitation attendance (% continuous): |                          |         |
| Mail-outs (n=829) | 4.33 (3.60 to 9.27) | 0.09 |
| Mail-outs plus phone calls (n=844) | 10.9 (5.10 to 16.7) | <0.001 |
| Adherence to medication in past 30 days (number of drug classes with ≥6 days missed; 0-4): |                          |         |
| Mail-outs (n=829) | 0.97 (0.81 to 1.17) | 0.78 |
| Mail-outs plus phone calls (n=844) | 0.91 (0.75 to 1.12) | 0.38 |
| Adherence to medication to in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 0.97 (0.76 to 1.23) | 0.79 |
| Mail-outs plus phone calls (n=844) | 0.86 (0.68 to 1.10) | 0.24 |
| Statin adherence in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 1.02 (0.78 to 1.32) | 0.91 |
| Mail-outs plus phone calls (n=844) | 0.95 (0.73 to 1.24) | 0.73 |
| Antithrombotic adherence in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 0.85 (0.58 to 1.26) | 0.41 |
| Mail-outs plus phone calls (n=844) | 0.82 (0.58 to 1.16) | 0.25 |
| β-blocker adherence in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 1.02 (0.80 to 1.30) | 0.88 |
| Mail-outs plus phone calls (n=844) | 1.00 (0.79 to 1.27) | 0.99 |
| Angiotensin system inhibitor adherence in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 1.08 (0.85 to 1.38) | 0.51 |
| Mail-outs plus phone calls (n=844) | 1.08 (0.84 to 1.40) | 0.53 |
| Persistence with medication in all four classes (yes/no): |                          |         |
| Mail-outs (n=829) | 1.00 (0.79 to 1.25) | 0.97 |
| Mail-outs plus phone calls (n=844) | 0.96 (0.76 to 1.21) | 0.71 |
| Persistence with statins (yes/no): |                          |         |
| Mail-outs (n=829) | 1.00 (0.72 to 1.40) | 0.99 |
| Mail-outs plus phone calls (n=844) | 1.00 (0.75 to 1.32) | 0.99 |
| Persistence with antithrombolytic (yes/no): |                          |         |
| Mail-outs (n=829) | 0.77 (0.50 to 1.18) | 0.23 |
| Mail-outs plus phone calls (n=844) | 0.86 (0.57 to 1.31) | 0.49 |
| Persistence with β-blocker (yes/no): |                          |         |
| Mail-outs (n=829) | 1.01 (0.77 to 1.31) | 0.96 |
| Mail-outs plus phone calls (n=844) | 1.09 (0.82 to 1.46) | 0.54 |
| Persistence with angiotensin system inhibitor (yes/no): |                          |         |
| Mail-outs (n=829) | 1.04 (0.83 to 1.31) | 0.74 |
| Mail-outs plus phone calls (n=844) | 1.08 (0.84 to 1.40) | 0.53 |
| Adherence to dual antiplatelets in past 7 days (yes/no): |                          |         |
| Mail-outs (n=829) | 0.97 (0.78 to 1.20) | 0.76 |
| Mail-outs plus phone calls (n=844) | 1.00 (0.80 to 1.26) | 0.97 |
| Quality of life (continuous): |                          |         |
| Mail-outs (n=829) | 0.09 (−1.38 to 1.54) | 0.91 |
| Mail-outs plus phone calls (n=844) | −1.00 (−2.73 to 0.72) | 0.25 |
| Smoking status (yes/no): |                          |         |
| Mail-outs (n=829) | 1.02 (0.73 to 1.42) | 0.91 |
| Mail-outs plus phone calls (n=844) | 1.03 (0.75 to 1.40) | 0.87 |
| **Administrative claims†‡ (n=1406)** |                          |         |
| Adherence to medication†‡ – PDC ≥80% (yes/no): |                          |         |
| Mail-outs (n=482) | 1.14 (0.87 to 1.49) | 0.35 |
| Mail-outs plus phone calls (n=450) | 0.99 (0.75 to 1.30) | 0.95 |
| Adherence to statins – PDC ≥80% (yes/no): |                          |         |
| Mail-outs (n=482) | 0.89 (0.69 to 1.16) | 0.39 |
| Mail-outs plus phone calls (n=450) | 1.04 (0.80 to 1.36) | 0.78 |
| Adherence to antithrombolytic†‡ – PDC ≥80% (yes/no): |                          |         |
| Mail-outs (n=482) | 1.09 (0.85 to 1.41) | 0.51 |
| Mail-outs plus phone calls (n=450) | 1.10 (0.85 to 1.43) | 0.48 |
| Adherence to β-blocker – PDC ≥80% (yes/no): |                          |         |
| Mail-outs (n=482) | 0.91 (0.70 to 1.17) | 0.48 |
| Mail-outs plus phone calls (n=450) | 0.99 (0.76 to 1.29) | 0.95 |

(Continued)
Table 4 | Continued

| Source, outcome, and intervention* | Effect estimate† (95% CI) | P value |
|-----------------------------------|---------------------------|---------|
| Adherence to angiotensin system inhibitor – PDC ≥80% (yes/no): | | |
| Mail-outs§ (n=482) | 1.02 (0.79 to 1.31) | 0.89 |
| Mail-outs plus phone calls§ (n=450) | 0.95 (0.73 to 1.23) | 0.71 |
| Administrative claims** (n=2624) | | |
| No of outpatient visits: | | |
| Mail-outs§ (n=874) | 1.03 (0.97 to 1.10) | 0.36 |
| Mail-outs plus phone calls§ (n=875) | 1.03 (0.97 to 1.09) | 0.33 |
| No of emergency department visits without admission: | | |
| Mail-outs§ (n=874) | 1.27 (1.08 to 1.48) | 0.003 |
| Mail-outs plus phone calls§ (n=875) | 1.08 (0.92 to 1.26) | 0.34 |
| No of hospital admissions: | | |
| Mail-outs§ (n=874) | 1.05 (0.90 to 1.23) | 0.55 |
| Mail-outs plus phone calls§ (n=875) | 1.02 (0.87 to 1.19) | 0.82 |
| Repeat myocardial infarction, stroke, or coronary revascularisation (yes/no): | | |
| Mail-outs§ (n=874) | 0.96 (0.73 to 1.27) | 0.79 |
| Mail-outs plus phone calls§ (n=875) | 0.89 (0.68 to 1.18) | 0.41 |
| All cause mortality‡‡: | | |
| Mail-outs§ (n=874) | 0.98 (0.67 to 1.45) | 0.93 |
| Mail-outs plus phone calls§ (n=875) | 0.67 (0.43 to 1.03) | 0.07 |

PDC=proportion of days covered. All effect estimates are adjusted for fixed effect of centre (stratifying factor in randomisation). Fully conditional specification was used to create 20 imputed datasets for each outcome (that is, multiple imputation). These multiple datasets were then analysed independently using regression analysis. The effect estimates and 95% confidence intervals presented were obtained by pooling regression results across the imputed datasets using Rubin’s rules (see statistical appendix for more details).

*Reference group=usual care.
†Effect estimate is an absolute mean difference for continuous outcomes (β=MD), odds ratio for categorical outcomes (exp[β]=OR), rate ratio for count-based outcomes (exp[β]=RR), and hazard ratio (exp[β]=HR) for all cause mortality (which was modelled as a time-to-event outcome).
‡Includes individuals who died between 28 and 365 days after randomisation.
§Excludes individuals who died before 28 days after randomisation.
¶Limited to 1412 older adults (65 and older) in initial sample. Six participants not used in sample owing to inability to link their patient reported data with administrative claims data.
**Smaller number than the patient reported sample for co-primary outcomes (n=2632) due to inability to link their patient reported data with administrative claims data.
***Occurrence of death and death date obtained from administrative (that is, Ontario Registered Persons Database) claims.

immediately after myocardial infarction, but other Ontario studies suggest that after myocardial infarction most patients are discharged with prescriptions for all relevant drug classes, which is why this trial focused on supporting long term adherence. The reliance on administrative data and a single patient report at the time of outcome meant that intermediate clinical outcomes, such as cholesterol levels or blood pressure, were not available. Furthermore, while the approach mimicked one which the health system might use, some enrolled patients did not meet eligibility criteria, leading to exclusions after randomisation. Likewise, the loss to follow-up was higher than expected, and differential dropout across arms could have been a function of the highly pragmatic approach (eFigure 1). Since no consent was obtained before randomisation and because each intervention contact offered an option to opt out, it is not surprising that the intervention with most contact—phone calls—led to more patients ending their participation. Although, loss to follow-up was greater than expected, it is reassuring that the intervention was centrally administered and adherence to medication, which was lower in the usual care group, mitigated the impact of loss to follow-up on the power of this trial. Many people do not like automated calls; it is possible that up front consent would have reduced the dropout rate in the mail plus phone group. Such consent, however, could have biased the population and resulted in a less conservative effect estimate than could be achieved by the health system if they used an intervention similar to that tested in this trial as part of their routine processes.

An embedded process evaluation, to be published separately, was conducted to explore mechanism(s) of action and to understand more about loss to follow-up. In this study, we could not use text messages, email, or web applications (apps) to support adherence to medication, because contact details, such as mobile phone numbers and email addresses, were not available in the routinely collected administrative data. Text, email, or apps might have been more effective than postal and telephone based interventions, especially if the timing and content of messages could have been personalised, because home telephones and postal mail are increasingly being replaced with digital communications. Further research is warranted. Complete evaluation of cost effectiveness was beyond the scope of this paper, but it should be noted that the intervention was centrally administered using pre-existing provincial databases. This process lends to the feasibility of scaling the intervention and its potential cost effectiveness if clinical events could be averted through increased completion of cardiac rehabilitation, as suggested by the literature. Finally, one of the mechanisms through which rehabilitation might reduce morbidity and mortality could be through encouraging adherence to medication, but the study was underpowered to evaluate this interaction. Possibly, variability in the content and delivery of cardiac rehabilitation in Ontario could have limited its effect on quality of life or on subsequent events in this study.

Conclusion

This pragmatic, three arm, single blinded, multicentre randomised trial across provinces showed that interventions informed by behavioural theory and patient input delivered by both mail and phone can significantly increase attendance and completion of cardiac rehabilitation after myocardial infarction, but not adherence to medication. In learning health systems, routinely collected data should support programme delivery (and vice versa); this study shows both the opportunities and the challenges of using registry data to support system-wide trials of quality improvement. This trial also demonstrates how a system level, centralised intervention efficiently supported programme delivery (and vice versa); this study shows both the opportunities and the challenges of using registry data to support system-wide trials of quality improvement. This trial also demonstrates how a system level, centralised intervention efficiently supported programme delivery and postal mail are increasingly being replaced with digital communications. Further research is warranted. Complete evaluation of cost effectiveness was beyond the scope of this paper, but it should be noted that the intervention was centrally administered using pre-existing provincial databases. This process lends to the feasibility of scaling the intervention and its potential cost effectiveness if clinical events could be averted through increased completion of cardiac rehabilitation, as suggested by the literature. Finally, one of the mechanisms through which rehabilitation might reduce morbidity and mortality could be through encouraging adherence to medication, but the study was underpowered to evaluate this interaction. Possibly, variability in the content and delivery of cardiac rehabilitation in Ontario could have limited its effect on quality of life or on subsequent events in this study.

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Data sharing: Individual, de-identified participant study data, and the data dictionary will be shared upon reasonable request to pursue additional studies or for replication, with the exception of data from administrative databases, which must be accessed through ICES.

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Supplementary material
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Web appendix: Supplementary material