Effectiveness and Safety of Early Initiation of Poststernotomy Cardiac Rehabilitation Exercise Training: The SCAR Randomized Clinical Trial

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Early initiation of post-sternotomy cardiac rehabilitation exercise training (SCAR): A randomized clinical trial.

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KEY POINTS

Question

Is starting cardiac rehabilitation exercise training two weeks post-sternotomy as effective and safe as starting six weeks post-sternotomy?

Findings

In this assessor blind, non-inferiority trial of 158 cardiac surgery patients, starting cardiac rehabilitation exercise training two weeks post-sternotomy was as effective, and likely as safe, as starting six weeks post-sternotomy.

Meaning

Adopting a progressive individualized approach, cardiac surgery sternotomy patients can start cardiac rehabilitation exercise training up to four weeks earlier than current guidance, and thus potentially complete their recovery sooner.

Abstract

IMPORTANCE

Guidelines recommend that cardiac rehabilitation exercise training should not start until six weeks post-sternotomy, although this is not evidence based. Limited data suggest starting earlier is not detrimental, but clinical trials are needed.

OBJECTIVE

To compare the effectiveness and safety of cardiac rehabilitation exercise training started either two weeks (early CR) or six weeks (usual care CR) post-sternotomy.

DESIGN

Assessor-blind, parallel group, non-inferiority, randomized controlled trial, recruiting July 2017 to March 2020.

SETTING

Two outpatient National Health Service rehabilitation centres; University Hospital, Coventry, and Hospital of St Cross, Rugby, UK.

PARTICIPANTS

Consecutive cardiac surgery sternotomy patients. Of 497 patients screened, 139 were ineligible due to surgical complications or co-morbidities, and 200 declined participation.

INTERVENTION

Participants were randomized to eight weeks of twice-weekly supervised cardiac rehabilitation exercise training starting either two weeks (early CR) or six weeks (usual care CR) post-sternotomy. Exercise training adhered to existing guidelines, including functional strength and cardiovascular components.

MAIN OUTCOMES AND MEASURES

Outcomes were assessed at baseline (in-patient post-surgery), post-cardiac rehabilitation (10 or 14 weeks post-sternotomy), and 12 months post-randomization. The primary outcome was the change in six-minute walk test distance from baseline to post-cardiac rehabilitation. Secondary outcomes included safety, functional fitness and quality of life.

RESULTS

158 participants (133 male [84.2%], 25 female [15.8%]; age, 63 [SD:11.5] years) were randomized, and 118 (61 usual care CR; 57 early CR) were included in the primary analysis. Early CR was not inferior to usual care CR (non-inferiority margin 35m); the mean change in six-minute walk distance from baseline to post-cardiac rehabilitation was 28 metres greater in the early CR group, (95%CI, -11 to 66, p=0.162). Mean differences for secondary outcomes were not statistically significant, indicating non-inferiority of early CR. There were 46 vs 58 (p=0.) adverse events and 14 vs 18 (p=0.) serious adverse events in usual care CR and early CR respectively.

CONCLUSIONS AND RELEVANCE

Starting exercise training from two weeks post-sternotomy was as effective as starting six weeks post-sternotomy for improving six-minute walk distance. With appropriate precautions, clinicians and cardiac rehabilitation professionals can consider starting exercise training as early as two weeks post-sternotomy.

Trial Registration number: NCT03223558

https://clinicaltrials.gov/ct2/show/NCT03223558

Introduction

In the United Kingdom (UK), approximately 35,000 patients annually have cardiac surgery requiring median sternotomy (1). Improvements in post-operative care and reduced complication rates have resulted in shorter length-of-stay; five-seven days on average (2). Despite this, cardiac rehabilitation is not currently started until six weeks post-sternotomy due to concerns about adequate sternal healing (3). With a lack of evidence relating to activity following median sternotomy, clinical recommendations are often conflicting, arbitrary and anecdotal, thus potentially overly restrictive. The six-week sedentary period at home post-sternotomy may be a missed opportunity for structured rehabilitation and faster recovery.

The British Association for Cardiovascular Prevention and Rehabilitation (BACPR) (4) recommends early cardiac rehabilitation, although this is not clearly defined. A delay in starting cardiac rehabilitation is known to prolong recovery, increase dependence on family/carers, and cause frustration, particularly for those of working age (5, 6). This can contribute to anxiety and depression after cardiac surgery. Furthermore, any delay can attenuate the benefits of cardiac rehabilitation (7) and negatively affect compliance and adherence if the patient perceives the need for rehabilitation has passed.

Evidence from several studies suggests that overly restrictive sternal precautions may in fact contribute to poor health, particularly in the elderly (6, 8, 9). Furthermore, intra-thoracic pressures generated by coughing and sneezing were reported to be more excessive than most daily activities that patients are currently advised to avoid (10). Many patients rapidly lose muscle and bone mass during post-sternotomy

sedentary periods (11), increasing the risk of falls and prolonging recovery. Accordingly, a number of preliminary studies have demonstrated superior outcomes when beginning activity earlier post-sternotomy (5, 12-15).

Despite advances in post-sternotomy care, there are no accepted evidence-based recommendations to guide clinicians and cardiac rehabilitation professionals. This has resulted in the unsatisfactory situation of consensus opinion rather than empirical evidence guiding clinical care. There are no good quality prospective trials that have assessed the effectiveness and safety of earlier initiation of cardiac rehabilitation exercise training post-sternotomy for cardiac surgery.

The objective of this randomized clinical trial was to investigate the effectiveness and safety of cardiac rehabilitation exercise training started two weeks post-sternotomy (early CR) compared with six weeks post-sternotomy (usual care CR). We hypothesised that early CR would be as effective and safe as usual care CR.

Methods

Trial Design/setting

The SCAR study was a pragmatic, assessor-blind, parallel group, randomized controlled non-inferiority trial, conducted in a real-world UK National Health Service (NHS) outpatient cardiac rehabilitation service. The trial protocol is published in full elsewhere (16) and in supplementary material. The trial was approved by Edgbaston Research Ethics Committee (17/WM/0057) on 12th April 2017 and registered with ClinicalTrials.gov: NCT03223558 on 19th July 2017.

Study Participants

Recruitment took place between July 2017 and March 2020. Coronary artery bypass graft and mitral/aortic valve replacement/repair patients recovering from median sternotomy at University Hospital, Coventry were eligible. Inclusion criteria included: age 18-90yrs, and able to provide written informed consent. Patients were excluded for the following reasons: serious compromising cardiac arrhythmias; neurological disorders; significant co-morbidities that would prevent full participation; and inability to enroll for the full duration the trial. Transport to and from the cardiac rehabilitation facility was offered to participants who had no other means of travel. Following sternotomy, patients were not permitted to drive in line with UK post-surgical Driving and Vehicle Licensing Agency restrictions (17).

Randomization and blinding

Participants were randomized to early CR or usual care CR, on a 1:1 basis, via block randomization. The random allocation sequence was generated by the trial statistician and implemented by an independent clinician. To ensure allocation concealment, randomization requests were submitted further to completion of all baseline assessments, post-surgery. Outcome assessors and cardiac surgeons were blind to group allocation. It was not possible for participants and cardiac rehabilitation professionals involved in the exercise training interventions to be blind to group allocation.

Interventions

Participants in both trial arms completed eight weeks of twice weekly, one-hour, cardiac rehabilitation exercise training, with equal supervision.

Usual care cardiac rehabilitation (six weeks post-sternotomy)

Locally produced written home exercise guidance was provided for six weeks preceding enrolment, recommending short bouts (five minutes) of light–moderate intensity walking, progressing in duration each week. In addition, a series of shoulder mobility exercises were recommended, with the advice to avoid pain and/or undue post-exercise fatigue. At six weeks, usual care CR adhered to UK standards (BACPR/ACPICR, Association of Chartered Physiotherapists in Cardiac Rehabilitation) (4, 18). Briefly, a 15-minute warm-up with light cardiovascular and mobility exercises (<40% heart rate reserve (HRR) was followed by 20–40 minutes of moderate intensity continuous cardiovascular exercise (e.g., cycle ergometer, rowing ergometer, treadmill, walking track) at 40%–70% HRR. After a 10-minute cool down, functional muscular strength, flexibility and proprioception exercises were undertaken (e.g., resistance machines, free weights, multi-plane functional exercises). Upper body exercises were performed carefully to avoid sternal and leg wound pain and complications. Exercise duration and workload were increased, as tolerated, based on heart rate and participant reported Rating of Perceived Exertion (RPE).

Early cardiac rehabilitation (two weeks post-sternotomy)

There are no specific outpatient cardiac rehabilitation exercise prescription guidelines for patients who have undergone recent sternotomy (<6 weeks). In the first two to three weeks of early CR, participants followed an individualized exercise programme dictated by their current level of fitness and post-surgery symptoms and limitations. Light shoulder and chest mobility and strength exercises were introduced

when participants were able to perform them with minimal discomfort, with moderate intensity cardiovascular interval training started in parallel. By weeks two to three of early CR, participants progressed towards achieving current UK standards as per usual care CR above.

Outcomes

Outcomes were measured at three time-points; 1) baseline (in-patient post-surgery pre-randomisation); 2) post-rehabilitation after the eight-week cardiac rehabilitation programme (~10 weeks post-surgery for early CR and ~14 weeks post-surgery for usual care CR); and 3) 12 months post-randomization.

Primary outcome

The primary outcome was the change in six-minute walk test (6-MWT) distance from baseline to post-rehabilitation. The 6-MWT was conducted in accordance with guidelines (19). Participants walked, self-paced, along a 30m walking track for six minutes. The primary outcome was calculated as the post-rehabilitation measurement, minus the baseline measurement so that a positive value corresponded to an improvement, and a negative value to a deterioration.

Secondary outcomes

To assess functional lower extremity muscular strength and power, the Five-Times Sit to Stand (5T-STS) test was performed (20). Leg strength was further evaluated with isometric dynamometry (PCE FB1k dynamometer, PCE instruments, Germany); the force generated during a resisted leg extension was measured for both limbs,

and the highest value recorded (21). Digital hand-held dynamometry (JAMAR plus, Performance International Limited, UK) was undertaken to measure hand grip strength in both limbs, adhering to the American Society of Hand Therapists recommendations (22). Participants were instructed to perform a maximal grip contraction for two to five seconds; the highest of three attempts was recorded.

Anxiety and depression were measured with the seven item Generalized Anxiety Disorder (GAD-7) and nine-item Patient Health Questionnaire (PHQ-9) respectively (23). The Short Form Survey (SF-12) were used to evaluate HR-QoL, providing values for mental, physical, and total health (24).

Compliance and adherence were evaluated by recording the number of cardiac rehabilitation sessions completed and reasons for drop-out. To assess the safety of early CR, adverse and serious adverse events were defined *a priori* and monitored in line with the international principles of Good Clinical Practice (25) . By convention, serious adverse events were recorded from randomisation, and classified as any untoward medical occurrence that resulted in death, was immediately life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity (25).

Sample size

As described elsewhere (16), to achieve 90% power, 60 participants were required in each trial arm to assess the non-inferiority of early CR compared to usual care CR,

based on the mean difference of 6-MWT changes from baseline to post-rehabilitation (primary outcome). The non-inferiority margin was 35 metres (m) and the mean 6-MWT changes for early and usual care CR were assumed equal. Based on existing data (26), a common standard deviation of 65m was assumed. A target sample size of 140 participants (70 in each arm) was required to allow for 15% dropout. During the study, dropout rate was higher than expected (22% for early CR and 29% for usual care CR), therefore, the sample size was revised to 170 participants. The trial was not powered to confirm the non-inferiority of secondary outcomes.

Statistical analysis

Data are summarised and reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guideline (27). Statistical analyses were performed in R (28). To compare categorical baseline characteristics for early CR and usual care CR, counts, percentages and chi-squared tests were used. Mean (standard deviation), median (interquartile range) and Mann-Whitney U tests were used to compare baseline ordinal and continuous characteristics.

A t-test (primary analysis) was used to compare mean 6-MWT changes at post-rehabilitation from baseline (primary outcome) for early CR and usual care CR. The 95% confidence interval (CI) from the analysis was used to determine if early CR was non-inferior to usual care CR (26). Similarly, for each secondary outcome, a t-test was used to compare the mean changes for early CR and usual care CR. Non-inferiority margins were not pre-specified for secondary outcomes. Before using a t-test, normality of outcome values in usual care CR and early CR was assessed using a Shapiro-Wilk test and histogram. A post-hoc ANCOVA model, adjusting for

the baseline 6-MWT distance, was fitted to compare mean 6-MWT distance changes at post-rehabilitation from baseline (primary outcome) for early CR and usual care CR.

Pre-planned secondary analysis was to fit a linear mixed model (LMM) for each outcome with measurements taken at all assessment visits. However, after noting that measurements at each assessment visit were not approximately normally distributed, multiple imputation was preferred with chained equations using the MICE package (29) in R since both assume values are missing at random. Three deceased participants (one in early CR; two in usual care CR) were not included in multiple imputation.

Secondary outcomes were derived by calculating the change post-rehabilitation from baseline. Changes were approximately normally distributed and computed so that a positive change corresponded to an improvement and a negative change to a deterioration, except for 5T-STS, GAD-7, and PHQ-9, where the reverse occurs.

Results

Participant characteristics

A total of 497 patients met the inclusion criteria at University Hospital Coventry and Warwickshire (UHCW) NHS trust between June 2017 and January 2020 (Figure 1) 339 patients were excluded, mainly due to surgical complications and unwillingness to take part. In total, 158 participants were randomized. Baseline characteristics for usual care CR (n=80) and early CR (n=78) were balanced for demographics and

comorbidities (Table 1). Baseline characteristics were also similar between completers (n=118) and participants lost to follow-up (n=40) (eTable S1).

Primary Outcome

At baseline, the mean 6-MWT distance for early CR (209.1 [117.6] m) was lower than for usual care CR (243.9 [144.2] m, *p*=0.116) (Figure 2). Post-rehabilitation, the mean 6-MWT distance for early CR was similar to usual care CR, showing a greater increase in 6-MWT distance for early CR compared to usual care CR (275.0 [148.5] m vs 247.5 [146.6] m, *p*=0.676). Early CR was not inferior to usual care CR (difference in mean change for 6-MWT, 28m [95% CI, -11 to 66], *p*=0.162) (Figure 2 & Table 2) and the improvement with early CR was achieved four weeks earlier in the recovery timeline. Post-hoc ANCOVA confirmed these findings (adjusted difference in mean change for 6-MWT distance; 8m, 95% CI, -20 to 36, p=0.584).

Secondary Outcomes

For both early CR and usual care CR, there were improvements in all secondary outcomes from baseline to post-rehabilitation (Table 2). Mean differences between groups for all secondary outcomes were not statistically significant, indicating the non-inferiority of early CR. For leg strength, GAD-7, PHQ-9, and SF-12 mental and total, mean improvements for early CR were greater than for usual care CR, while for 5T-STS, grip strength and SF-12 physical, mean improvements for usual care CR were greater than for early CR.

The Covid-19 pandemic substantially impeded collection of 12-month follow-up data. For all outcomes, complete case analysis of changes at 12 months from baseline did

not show statistically significant differences between early CR and usual care CR (eTable S2).

Adherence and safety

Fifty-six (67.5%) participants in usual care CR, and 58 (74%) in early CR completed at least 80% (13/16) of scheduled sessions. The mean number of sessions completed was 11 (SD, 5.6) in usual care CR, and 11 (SD, 5.4) in early CR. Reasons for drop-out between randomization and the primary outcome time-point for usual care CR and early CR respectively included returned to work (n= 1, 1), medical (n= 6, 7), unable to attend (n= 10, 7), died (n= 2, 1), Covid-19 pandemic (n= 4, 1).

There were 46 adverse events in usual care CR and 58 in early CR (p=0) (Table 3). Further, Eight adverse events, including muscular soreness, shortness of breath on exertion, and arrhythmia, were related to the interventions in both usual care CR and early CR. tThere were 14 serious adverse events in usual care CR and 18 in early CR (p=0) (table 3). These included expected events e.g., death, respiratory infection, cardiac arrhythmia, sternal instability and superficial sternal infection; and unexpected events e.g., road traffic accident, gastroenteritis (table S3). However, in accordance with our protocol, and as ratified by a cardiac surgeon, none of these were deemed to be related to the interventions. Of note, Tthere were four sternal wound complications in early CR compared toand only one in usual care CR,. hHowever, all of these eventsinstances were identified and resolvedoccurred prior to the commencement of CR and were thus categorically unrelated to the interventions.exercise training.

Discussion

In this randomized clinical trial, starting cardiac rehabilitation exercise training as early as two weeks post-sternotomy (early CR) was as effective as starting six weeks post-sternotomy (usual care CR). Effectiveness was demonstrated primarily by there being no difference between the two trial arms in the change in 6-MWT distance from baseline to post-rehabilitation. Importantly, the early CR group achieved the same improvement as the usual care CR group up to four weeks earlier in their recovery. The safety of early CR, whilst not proven definitely, was underlined by there being no statistical difference between the two trial arms in the number of adverse and serious adverse events. Existing guidelines based on consensus opinion recommend abstinence from cardiac rehabilitation exercise training for six weeks post-sternotomy. Data from the current trial lend support to starting as early as two weeks post-sternotomy.

Commented [GM1]: ?? correct

To our knowledge, the present study is the first prospective trial to test the effectiveness and safety of early initiation of post-sternotomy cardiac rehabilitation. Our findings support previous observational studies (5, 10, 12, 30). By starting as early as two weeks post-sternotomy, the non-inferiority design of our trial enabled us to assess if these previously reported benefits could be safely achieved up to four weeks earlier than current usual care clinical practice. Gaining the physical and psychosocial benefits of rehabilitation up to four weeks earlier at no additional risk to recovery, has significant implications for patients undergoing median sternotomy. Social function and economic productivity can be restored more quickly, leading to a substantial positive impact on quality of life (6). In addition, clinicians can ~~confidently~~

now advocate earlier rehabilitation based on empirical evidence rather than consensus opinion. Providing a progressive individualized approach is taken, rehabilitation professionals can now feel assured in removing many of the unhelpful restrictions that may have previously hindered patients' recovery.

In addition to the non-inferiority of early CR in 6-MWT distance, our trial also demonstrated equal improvement in all other clinical, physical and quality of life outcomes. These findings indicate the holistic benefit of early CR. Further, long-term recovery was consistent between trial arms; over 12 months, 6-MWT distance improved equally in both groups. It should be noted that our sample size at 12 months was impacted considerably by the Covid-19 pandemic, preventing long-term follow-up in 35 participants.

Our findings confirm previous reports highlighting the potential benefits of relaxing restrictive sternal precautions post-operatively. The 'Keep Your Move in the Tube' sternal guidance (5) has been shown to improve outcomes (15, 30, 31), and a recent review concluded that controlled upper body activity, individualized progressive functional activity, and less restrictive precautions, promoted better recovery (12). Despite these findings, many guidelines remain restrictive. Data from the current trial can inform new guidelines.

Although we have shown that sternotomy patients can participate in earlier cardiac rehabilitation, work is required to reassure patients that this is beneficial and safe. Of the 497 patients screened, 200 (40%) did not wish to take part. This low uptake could relate to fear of harm with earlier cardiac rehabilitation as well as disinterest in

research during life changing circumstances. Patients' beliefs are directly influenced by the healthcare advice they receive (32). Therefore, dissemination of the lack of evidence supporting restrictive precautions in this population, to all surgical and healthcare professionals involved in sternotomy patient care, is essential. If surgical teams inform patients at the initial pre-operative consultation, that early post-sternotomy cardiac rehabilitation is in their best interests, it is likely that there would fewer objections or concerns.

There were more serious adverse events in the early CR group, however, these related to prolongation of post-surgery hospitalization prior to starting cardiac rehabilitation rather than resulting from participation in exercise training. Whilst we also recorded more adverse events with early CR, we believe this can be attributed to more regular contact with this group in the early stages of recovery

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be attributed to more regular contact with this group in the early stages
of recovery resulting in more opportunity for participants to discuss minor medical complaints that may otherwise have resolved without the intervention of a healthcare professional.

Limitations

This was a pragmatic trial in a real-world clinical setting, thus results are clinically relevant to post-sternotomy care and cardiac rehabilitation around the world. However, although participants were recruited from a wide geographical area and completed their cardiac rehabilitation at one of two facilities, this was essentially a

single-center trial. Results may not be representative of the UK as a whole, and the population was primarily male (85%), although this is indicative of the cardiac surgery population (33). A considerable proportion of 12-month data were missing due to the Covid-19 pandemic, meaning we have lower confidence in our findings at 12 months. Nevertheless, we did achieve appropriate statistical power to confirm the effectiveness of early CR compared to usual care CR at our post-rehabilitation primary outcome time-point. Whilst we can, to some extent, confirm the safety of early CR compared to usual care CR, the trial was not powered specifically for safety outcomes.

Conclusions

In cardiac surgery patients undergoing median sternotomy, supervised cardiac rehabilitation exercise training started as early as two weeks post-sternotomy was as effective as starting at six weeks.

The physical and psychosocial benefits of cardiac rehabilitation were achieved up to four weeks earlier, allowing a faster return to social functioning and economic productivity. Providing a progressive, individualized approach is taken, clinicians and rehabilitation professionals can initiate exercise training as early as two weeks post-sternotomy.

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Contributions

Concept and design: SE, GM, GL, SW, TB, PB. *Data acquisition, analysis, interpretation*: GL, BE, RP, SE, SW, PKK, AJK, GM, TB, PB. *Manuscript drafting:* SE, GM, PKK. All authors critically reviewed the draft manuscript and approved the final version.

Data access

SE and GM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest disclosures

GM and PB have received research grants from the National Institute for Health Research and/or the British Heart Foundation. GM and SE are Directors of Atrium Health Ltd., a provider of rehabilitation services for the NHS.

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Table 1: Demographic and clinical characteristics

Characteristic / Outcome	Usual care CR (n=80)	Early CR (n=78)	p-value
Demographic characteristics			
Gender, n (%) Females	9 (11.25)	16 (20.51)	0.111‡
Age (years) at surgery Mean (SD) Median (IQR)	 64.04 (10.3) 66.00 (58.0-72.2)	 61.56 (12.6) 64.00 (56.0-70.0)	0.284*
Body Mass Index (BMI) Mean (SD) Median (IQR)	 28.63 (4.9) 27.66 (25.67-30.99)	 29.29 (5.7) 28.45 (25.05-32.72)	0.416*
Surgery, n (%) Elective Emergency	 56 (70) 24 (30)	 49 (62.8) 29 (37.2)	0.339‡
Procedure, n (%) CABG AVR/MVR CABG+AVR/MVR	 39 (48.7) 35 (43.8) 6 (7.5)	 32 (41.1) 39 (50) 7 (8.9)	0.619‡
Days surgery to randomisation	5.39 (1.56)	5.17 (1.62)	0.811
Past medical history			
Previous CABG, n (%) Yes	1 (1.2)	0 (0.0)	1.000**
IHD, n (%) Yes	24 (30.0)	14 (17.9)	0.076‡
Previous MI, n (%) Yes	10 (12.5)	12 (15.4)	0.601‡
Other past conditions, n (%) Yes	13 (16.7)	17 (21.2)	0.463‡
Current medical status			
Hypertension, n (%) Yes	39 (48.8)	32 (41.0)	0.329‡
Diabetes, n (%) Yes	12 (15.0)	21 (26.9)	0.065‡
Family history, n (%) Yes	18 (22.5)	12 (15.4)	0.254‡
HAD, n (%) Yes	3 (3.8)	3 (3.8)	1.000**
Smoking status, n (%) Non-smoker Smoker	 71 (88.8) 9 (11.2)	 67 (85.9) 11 (14.1)	0.590‡
Hypercholesterolaemia, n (%) Yes	25 (31.2)	24 (30.8)	0.948‡

Data as mean (standard deviation, SD) or median (interquartile range, IQR) as appropriate. ‡Chi-squared test; *Mann-Whitney U test; **Fisher's exact test; CABG, coronary artery bypass graft; AVR, aortic valve replacement; MVR, mitral valve replacement; IHD, ischaemic heart disease; MI, myocardial Infarction; HAD, hospital anxiety and depression score.

Table 2: Summary of results comparing changes from baseline to post-rehabilitation

Outcome	Complete case analysis							Multiple imputation
	n		Mean (SD) for usual care CR		Mean (SD) for early CR		Difference‡ (early CR – usual care CR) in changes	Difference‡ in changes (early CR – usual care CR)
	UCR	ECR	Baseline	Post-CR	Baseline	Post-CR	Mean (95% CI), p-value	Mean (95% CI), p-value
6-MWT (m)	57	61	243.9 (144.2)	491.4↑ (92.9)	209.1 (117.6)	484.1↑ (95.9)	27.5 (-11.2, 66.2), 0.162	27.7 (-9.9, 65.3), 0.149
5T-STS	55	58	19.27 (10.26)	9.33↑ (2.45)	18.42 (9.50)	9.07↑ (2.45)	-0.58 (-3.84, 2.67), 0.722	-0.57 (-3.56, 2.42), 0.709
Leg strength (Kg)	48	52	32.04 (13.17)	37.26↑ (13.89)	33.72 (11.51)	40.92↑ (13.71)	1.97 (-1.90, 5.84), 0.315	1.12 (-2.62, 4.87), 0.557
Grip strength (Kg)	56	59	32.48 (9.01)	36.42↑ (9.27)	32.17 (8.93)	35.01↑ (10.14)	-1.10 (-3.16, 0.96), 0.291	-0.98 (-3.02, 1.07), 0.351
GAD-7	44	55	5.18 (5.24)	1.55↑ (3.34)	5.95 (5.47)	1.35↑ (2.23)	0.96 (-0.99, 2.92), 0.331	1.00 (-0.81, 2.81), 0.278
PHQ-9	54	61	7.87 (5.64)	2.22↑ (3.00)	8.39 (5.78)	2.44↑ (3.05)	0.30 (-1.86, 2.47), 0.782	0.70 (-1.30, 2.70), 0.492
SF-12 Physical	37	47	12.03 (3.08)	16.38↑ (2.28)	11.51 (3.03)	15.53↑ (2.39)	-0.33 (-1.66, 1.00), 0.623	-0.71 (-1.88, 0.46), 0.237
SF-12 Mental	37	47	19.00 (4.55)	22.30↑ (3.74)	17.74 (3.93)	22.57↑ (3.00)	1.53 (-0.24, 3.30), 0.088	0.65 (-0.95, 2.26), 0.427
SF-12 Total	37	47	31.03 (7.01)	38.84↑ (5.26)	29.47 (6.28)	38.09↑ (4.47)	0.81 (-1.84, 3.46), 0.547	-0.39 (-2.73, 1.95), 0.746

Data as mean (standard deviation, SD) unless otherwise specified. UCR, usual care CR; ECR, early CR; 6-MWT, six-minute walk test distance; 5T-STS, five times sit-to-stand test; GAD-7, generalised anxiety disorder questionnaire; PHQ-9, patient health questionnaire; SF-12, short form survey; ↑ improvement; ↓ deterioration; ‡ positive and negative differences favour early CR and usual care CR respectively.

Table 3: Adverse events

	Usual care CR (n=80)	Early CR (n=78)
SAE		
Total (n)	14	18
Death	2	1
Sternal instability	1	4
Sternal wound infection	1	0
Musculoskeletal pain	1	2
TIA	1	2
LRTI	3	2
Fluid overload	2	0
Anaemia	1	1
Atrial Fibrillation	2	1
Endocarditis	0	1
Acute Kidney Injury	0	1
Pulmonary embolism	0	1
RTA	0	1
Eye casualty	0	1
AE		
Total (n)	46	58
Arrythmia	14	10
Superficial wound Infection	8	10
LRTI	4	9
Pleural effusion	5	0
Excessive SOB	1	8
Pre-syncope	2	2
Musculoskeletal pain	3	5
Fluid retention	1	2
Vertigo	0	1
UTI	2	1
Hypertension > 180/100	1	1
Haematuria	1	3
Leg wound bleed	0	1
Constipation	0	1
Osteoarthritis	0	1
PR bleed	0	1
DVT	1	0
Panic attack	1	0
Diarrhoea	0	1
Cellulitis	0	1
Epilepsy	1	0

Data as number (n). SAE, serious adverse event; AE, adverse event; TIA, transient ischemic attack; SOB, shortness of breath; LRTI, Lower Respiratory Tract Infection; RTA, Road Traffic Accident, UTI, Urinary Tract Infection; PR, Perirectal; DVT, deep vein thrombosis

Commented [GM2]: peter ? p values

Commented [GM3]: p value?

Figure 1. Consort Diagram

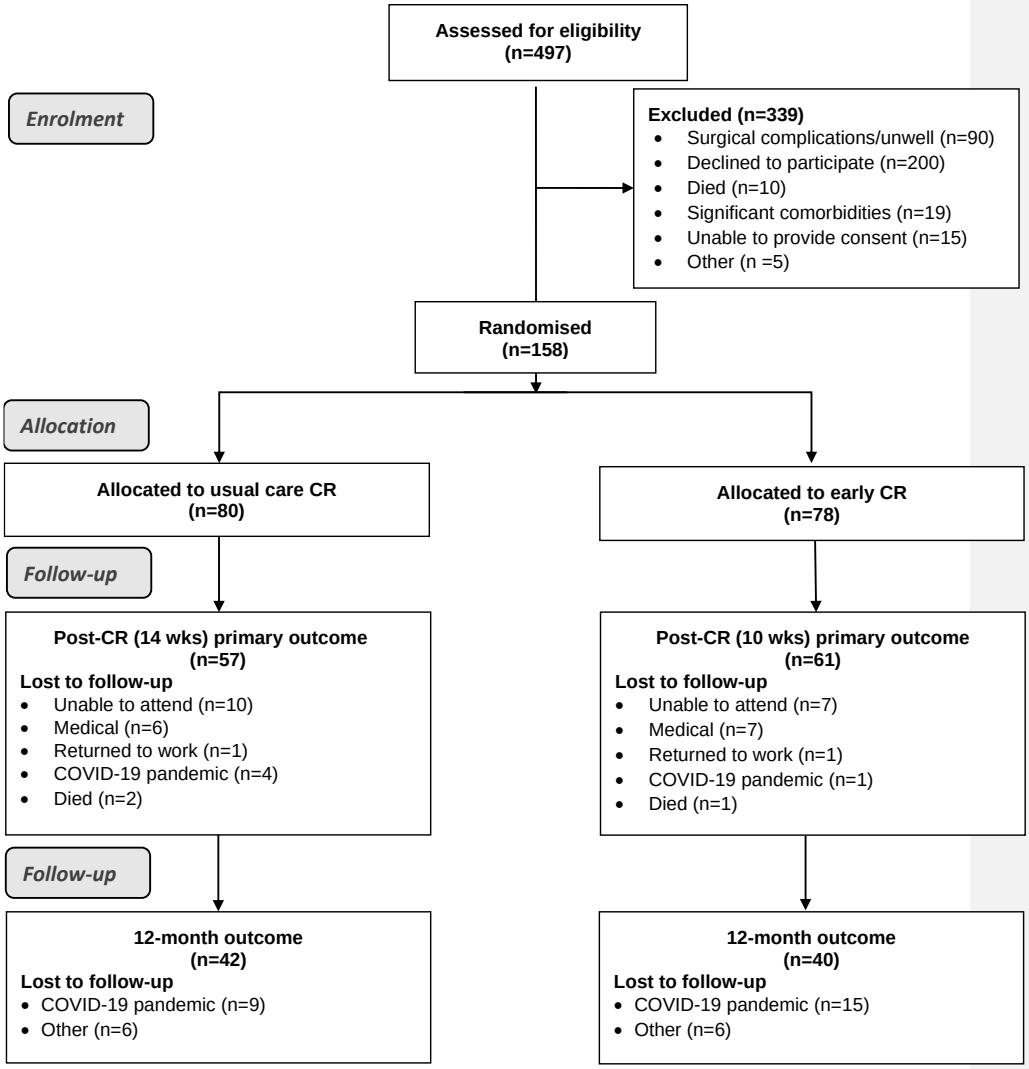
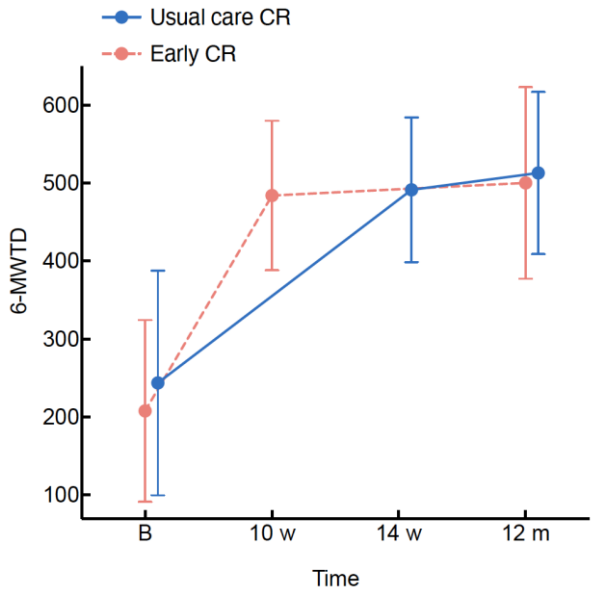


Figure 2. Primary outcome: change in 6MWT distance from baseline to post-rehabilitation and 12 months follow-up



Data as mean (SD). 6-MWT distance for early CR (blue line) and usual care CR (red line) at baseline, post-rehabilitation and 12 months.