General Hospital Psychiatry 94 (2025) 26–32

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: www.elsevier.com/locate/genhospsych

A randomized controlled trial of beta-blockers effects on cardiac anxiety

Philip Leissner [a,*,1], Katarina Mars [b,1], Sophia Humphries [a], Tomas Jernberg [c], Claes Held [d,e], Robin Hofmann [b], Erik M.G. Olsson [a]

[a] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[b] Department of Clinical Science and Education, Division of Cardiology, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden
[c] Department Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
[d] Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden
[e] Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden

ARTICLE INFO

Keywords:
beta-blocker
Cardiac anxiety
Randomized controlled trial
Myocardial infarction

ABSTRACT

Objective: Cardiac anxiety (CA) is common and has been associated with increased morbidity and mortality in patients after acute myocardial infarction (AMI). While beta-blockers are widely used in secondary prevention after AMI and have proven anxiolytic effects among psychiatric patients, little is known of their effect on CA among AMI-patients. This study aimed to investigate the effect of beta-blockers on CA in post-AMI patients with preserved cardiac function.

Methods: In this parallel-group, open-label, registry-based randomized clinical trial, assessments with the Cardiac Anxiety Questionnaire (CAQ) were obtained at hospitalization and at two follow-up points (6–10 weeks and 12–14 months) after AMI. Analyses were based on the intention-to-treat (ITT) principle using multiple linear regression, calculating both short- and long-term effects. Stratified analyses were also conducted in groups with low, moderate and high baseline values on the CAQ.

Results: From August 2018 through June 2022, 806 patients were enrolled. In the main analysis, no treatment effect of beta-blocker on CA was observed at either follow-up. In stratified analyses, the levels of CA symptoms were lower for those randomized to beta-blocker treatment in the group with moderate baseline CA, at follow-up 2 ($\beta = -0.12$; 95 % CI -0.22, −0.02; $P = 0.016$).

Conclusions: This trial found no evidence of an effect of beta-blockers on CA among AMI-patients with preserved cardiac function. However, lacking information on beta-blocker adherence limits the possibility of drawing firm conclusions. Furthermore, there might be a differential effect among patients depending on their baseline CA level, as patients with moderate baseline CA randomized to beta-blockers reported lower CA during follow-up than controls.

In the wake of an acute myocardial infarction (AMI), patients are commonly anxious about the recurrence of a cardiac event [1,2]. Beta-blockers have been a cornerstone in secondary prevention after MI in international guidelines for decades [3]. Moreover, studies have shown a beneficial effect of beta-blockers in lowering mortality and reinfarction in patients with heart failure after AMI [4] and they are also recommended as first line anti-anginal therapy in patients with chronic coronary syndrome [3]. However, beta-blockers are not only widely used in the spectrum of cardiac diseases [5,6,7], but have also been used for their anxiolytic effects and to reduce emotional arousal during stress [8,9].

The concern of recurrence of a cardiac event in patients after AMI often manifests in the form of anxiety, affecting around 20–40 % of the AMI-population [10,11]. In fact, this may not only impair quality of life, but anxiety disorders have been established as independent risk factors for the development of AMI and subsequent premature death [12,13]. Anxiety specifically pertaining to the fear of occurrence of a cardiac event is called cardiac anxiety (CA), also a significant prognostic factor for major adverse cardiac events in AMI patients [14,15]. CA is characterized by heightened awareness, fear, and avoidance of cardiac sensations, and its association with cardiovascular prognosis seems to be particularly driven by the aspect of behavioral avoidance [14,15]. While

* Corresponding author at: Uppsala University, MTC-huset, Dag Hammarskjölds väg 14B, Akademiska sjukhuset, 751 85 Uppsala, Sweden.
E-mail address: philip.leissner@uu.se (P. Leissner).
[1] Equal Scientific Contribution.

https://doi.org/10.1016/j.genhosppsych.2025.02.010
Received 11 December 2024; Received in revised form 12 February 2025; Accepted 12 February 2025
Available online 16 February 2025

behavioral avoidance is a natural reaction to injury, it may become chronic, leading to reduced self-efficacy and increased anxiety and withdrawal [16]. Fear of movement (i.e., kinesiophobia) is commonly observed among patients with coronary artery disease [17], driven by fear of overstimulating the heart. By reducing cardiac stimulation, e.g., with beta-blocker medication, it might be possible to interrupt the contributing and maintaining factors of CA.

Recent attention has focused on the use of beta-blockers in patients with ischemic heart disease, particularly those with preserved cardiac function after AMI. The Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction (REDUCE-AMI) trial recently demonstrated that long-term beta-blockers therapy in patients with AMI and preserved cardiac function did not significantly reduce the risk of recurrent cardiovascular events or mortality compared with no beta-blocker use [18]. This finding stands in contrast to data from landmark studies, which showed approximately a 20 % reduction in mortality with long-term beta-blocker use [19]. This discrepancy between findings is likely attributed to a lower proportion of large AMIs today and advances in modern treatment for AMI, including widespread use of percutaneous coronary intervention (PCI) and improved secondary preventive therapies [20].

To further assess the risk-benefit profile of beta-blocker therapy, substudies of the REDUCE-AMI trial have evaluated the effect of beta-blockers on quality of life and well-being, as well as anxiety and depression [21,22]. While a slightly increased risk for depression was noted [21], no differences in quality of life or general anxiety were observed [21,22]. However, questions remain regarding the impact of beta-blockers on the more specific anxiety symptoms of cardiac anxiety. Given the recent cardiac event, CA may be a more appropriate target for intervention. Not only may the reduced arousal lead to less symptoms of anxiety in itself, but may in turn reduce the frequency and intensity of triggers for cognitive symptoms, such as fear of recurrence and hypervigilance.

Thus, this exploratory, prespecified substudy of the REDUCE-AMI trial, aims to investigate whether the effects of long-term beta-blocker therapy may lead to reductions in self-reported CA, as measured by the cardiac anxiety questionnaire (CAQ), in patients with AMI and preserved cardiac function.

1. Method

1.1. Trial design and setting

This study is a prespecified, explorative, multicenter substudy of the REDUCE-AMI trial (ClinicalTrials.gov identifier NCT03278509), which was a prospective, open-label, parallel-group, registry-based randomized clinical trial. By incorporating a randomization procedure in a comprehensive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry [23,24]. Ethical approval was granted by the Ethical Review Board in Stockholm (dnr 2016/1707–31/4 and 2018/1048–32). In the REDUCE-AMI trial, patients were randomized to either beta-blocker treatment or no beta-blocker treatment. The design, rationale, and primary results of the main trial have been previously published [25,18]. Similarly, the design, rationale and primary findings of the quality-of-life substudies have also been previously published [26,21,22]. This paper presents data on self-reported levels of CA.

1.2. Participants and procedures

Patients were included in the REDUCE-AMI trial if: they were at least 18 years, had an AMI with obstructive coronary artery disease within 1–7 days, and provided written informed consent. Exclusion criteria included indication or contraindication to beta-blockers or any condition that affects patients' ability to follow study protocol. Further inclusion and exclusion criteria are reported in the main trial [18]. The patients who were randomized (1:1, stratified by trial center) in the main REDUCE-AMI trial, between August 2018 and June 2022 at eight Swedish hospital sites, were potentially eligible for inclusion in the current substudy. Included participants provided additional written informed consent for the substudy. Participants entered data online via a secure portal or on paper. Self-reported questionnaires were collected at baseline (within 7 days of the AMI), follow-up 1 (6–10 weeks post-AMI), and follow-up 2 (12–14 months post-AMI). Reminders were sent via email and text message, and unresponsive participants were contacted by phone. Paper questionnaires returned by mail were manually entered into the internet portal by research staff.

1.3. Sociodemographic and clinical characteristics

Data on age, sex, smoking status, and clinical characteristics were retrieved from the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry [27]. Information on death or emigration dates was obtained from the Swedish population registry [28].

Additional categorical variables were collected in a customized questionnaire and included: physically inactive (yes/no, less than one day per week of 30 min activity that elevates breathing and heart rate), smoking status (never; previous; current), psychotropic medication usage (yes, if needed; yes, regularly; yes, both regularly and if needed; no), education level (secondary school; high school; university/college up to 3 years; university/college longer than 3 years), country of birth (Sweden or elsewhere), relationship status (single; living with partner/married; living alone but in a relationship; other), belief about negative side effects of beta-blockers (yes; unsure; no), and self-reported beta-blocker usage at both follow-ups (yes; no; don't know).

1.4. Exposure

Patients in the beta-blocker group initiated metoprolol or bisoprolol treatment during their hospital stay and received prescriptions for continued use post-discharge. Physicians were encouraged to prescribe at least a moderate dose of Metoprolol (at least 100 mg) or Bisoprolol (at least 5 mg). Patients who were already on beta-blockers before accepting participation and randomized to no beta-blocker treatment received a tapering schedule over 2–4 weeks.

1.5. Outcome

The outcome assessed in this study was CA at both follow-up 1 and follow-up 2. CA was assessed with the cardiac anxiety questionnaire (CAQ) [29], consisting of 18 items rated on a 5-point Likert scale, ranging from 0 (never) to 4 (always). For comparable subscale scores, it is recommended to divide scores by the number of items [29], making the range between 0 and 4. The scale consists of the three subscales Fear, Avoidance, and Attention, a factor structure that has been found valid in Swedish post-MI patients [29,30]. In our sample, the internal consistency ranged from $\alpha = 0.84–0.80$ for the total score and the subscales Avoidance and Fear, and $\alpha = 0.63$ for the subscale Attention. The scale has demonstrated good convergent validity with other scales assessing anxiety and health phobia ($\rho = 0.50–0.77$) and also divergent validity towards general avoidance of daily activities and unrelated fear [29].

1.6. Sample size

Sample size was determined based on the aim to detect a standardized mean difference of 0.25 on the Hospital Anxiety and Depression Scale, as described in a previous publication [21]. We determined that 0.25 was a balanced and reasonable target. In previous studies using similar methodology and participants (e.g. [30]), the standard deviation

on the HADS was around 4, making it possible to detect a mean difference of 1 HADS point. While modest, this could still be clinically relevant at the group level. Accordingly, a sample size of 251 participants per group was calculated to be sufficient to detect this difference with 80 % power at a 5 % significance level. To increase power and account for potential cross-over and loss to follow-up, enrolment in the RQoL substudy extended beyond the initial target of 502 participants.

1.7. Statistical analysis

The main analysis followed the ITT principle. Descriptive statistics for continuous data are presented as mean and standard deviation (SD), while categorical and binary data are presented as numbers (N) and percentages (%). Group comparisons (stratified by baseline CAQ-levels) for baseline data were performed with ANOVA for continuous variables and Pearson's chi-squared test for categorical variables. Missing data, assumed to be missing at random (MAR), were handled using multiple imputation with chained equations and predictive mean matching, stratified by treatment arms [31]. Imputed values for individuals who died during follow-up were excluded from post-death follow-ups.

The main analyses consisted of two separate linear regression models, with randomization group as the independent variable, and CAQ Total scores at follow-up 1 and 2 as dependent variables. To enhance statistical power, the covariates baseline CAQ subscale scores, education, country of birth, age, and sex were included in the model. Additionally, identical analyses of CAQ subscales as dependent variables were also conducted to explore potential specific effects.

Two sensitivity analyses were conducted: First, using only complete cases and no imputation of missing data; Second, using self-reported beta-blocker adherence at the respective follow-up as exposure variable. For the latter, those who reported not knowing whether they were taking beta-blockers were coded as missing and all missing data were handled with multiple imputation.

Post-hoc, exploratory, analyses were conducted that were identical to the main analysis, but separately for participants with low, moderate and high baseline scores on the CAQ, respectively. Low was defined as a score < 1, reflecting an average rating of "never" to "rarely"; medium moderate was defined as a ≥ 1 and < 2, reflecting an average rating of "rarely" to "sometimes"; and high was defined as a score ≥ 2, reflecting an average rating of "sometimes" to "always".

Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were performed using Stata Software Package (version 18.0).

2. Results

2.1. Sample

A flowchart depicting the recruitment process is depicted in Fig. 1. Participants were enrolled between July 2018 and June 2022, and followed-up until July 2023. Out of the 806 included participants (mean age 64.7 ± 10.4 years; 77 % male), 4 died between follow-up 1 and follow-up 2. All baseline characteristics by exposure group are presented in Table 1.

Compared with the main study, the participants in this substudy were slightly older (64.7 years vs 63.3 years) and not as often current smokers (16 % vs 21 %), but did not differ in respect to any other baseline characteristic.

Notably, there was a statistically significant difference between groups regarding belief about unwanted beta-blocker side-effects. Additionally, baseline comparisons between those with low, moderate and high baseline CA were carried out (Appendix Table A1). Among these groups, differences were observed in respect of sex, hypertension, previous diagnosis of MI, previous prescription of beta-blockers, average systolic blood pressure, level of education, country of birth, psychotropic medication, and belief about beta-blocker side-effects.

At follow-up 1, 57 (7 %) reported being non-adherent and 167 (21 %) did not report adherence. At follow-up 2, 537 (67 %) and 77 (10 %) reported being non-adherent and 167 (21 %) did not report adherence.

For the outcome variable, at follow-up 1, data was complete for 667 (83 %), partially missing for 12 (1 %), and completely missing for 127 (16 %) participants. For the outcome variable, at follow-up 2, data was complete for 637 (79 %), partially missing for 19 (2 %), and completely missing for 150 (19 %) participants.

2.2. Main analysis

No evidence of a treatment effect was found for any of the CAQ

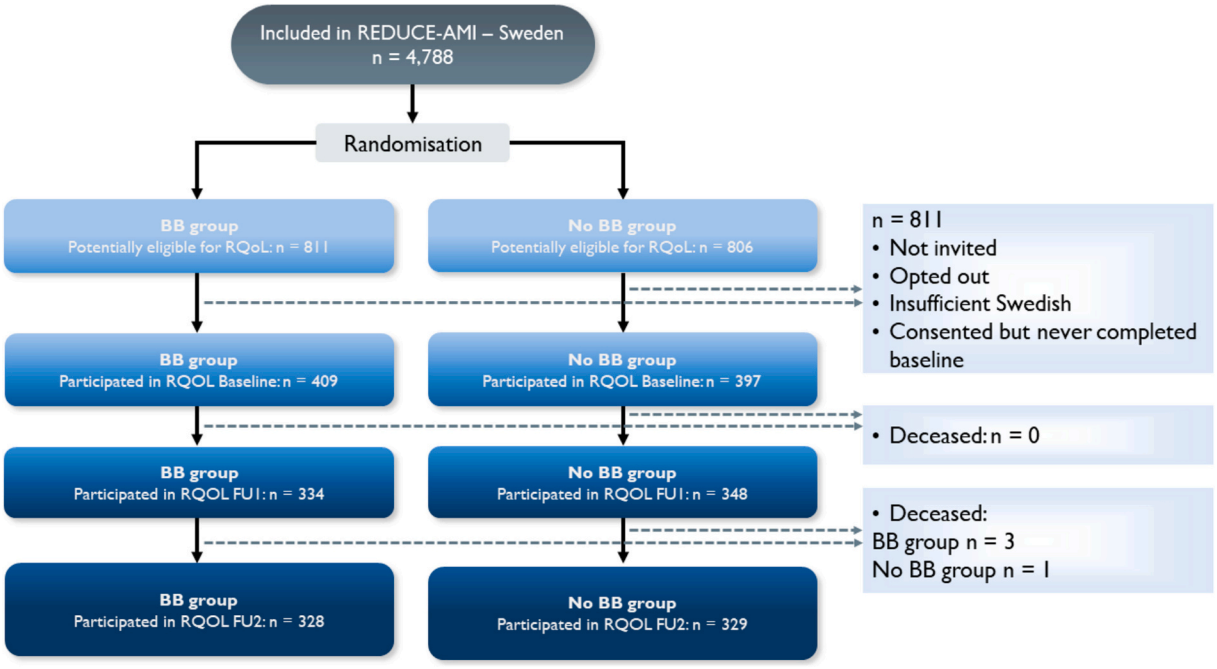

Fig. 1. Substudy flow chart.

Table 1
Descriptive statistics.

	Total (n = 806)	No Beta-blocker (n = 397)	Beta-blocker (n = 409)
Age, mean (SD)	64.7 (10.4)	64.2 (10.1)	65.2 (10.7)
Male, % (n)	77 % (624)	79 % (312)	76 % (312)
Hypertension, % (n)	50 % (400)	49 % (195)	50 % (205)
Previous diagnosis of diabetes, % (n)	16 % (128)	14 % (57)	17 % (71)
Previous PCI, % (n)	7 % (58)	7 % (29)	7 % (29)
Previous Stroke, % (n)	2 % (18)	2 % (8)	2 % (10)
Previous Myocardial Infarction, % (n)	8 % (63)	8 % (30)	8 % (33)
Degree of coronary artery disease			
1-vessel disease	54 % (406)	53 % (210)	54 % (219)
2-vessel disease	26 % (212)	26 % (102)	27 % (110)
3-vessel disease or left main	20 % (158)	21 % (82)	19 % (76)
Other	0 % (4)	0 % (2)	0 % (2)
Missing	0 % (3)	0 % (1)	0 % (2)
Type of beta-blocker medication, % (n)			
Bisoprolol			33 % (136)
Metoprolol			67 % (273)
Prior β-blocker prescription, % (n)	14 % (111)	14 % (56)	13 % (55)
Missing	0 % (1)	0 % (1)	0 % (0)
Systolic Blood Pressure, mean (SD)	151.2 (26.0)	151.5 (26.3)	150.8 (25.8)
Heart Rate, mean (SD)	74.9 (15.5)	74.6 (16.1)	75.2 (15.0)
Current Smoker, % (n)	16 % (132)	19 % (75)	14 % (57)
Missing	1 % (7)	1 % (3)	2 % (7)
Level of Education, % (n)			
Secondary School	21 % (172)	20 % (79)	23 % (93)
High School	42 % (341)	43 % (170)	42 % (171)
Undergraduate studies ≤3 years	19 % (153)	19 % (75)	19 % (78)
Undergraduate studies >3 years	17 % (138)	18 % (71)	16 % (67)
Missing	0 % (2)	0 % (2)	0 % (0)
In a relationship, % (n)	80 % (644)	79 % (315)	80 % (329)
Born in Sweden, % (n)	89 % (715)	88 % (351)	89 % (364)
Physically inactive at baseline, % (n)	31 % (244)	70 % (276)	68 % (280)
Missing	1 % (8)	0 % (2)	1 % (6)
Psychotropic medication for anxiety or depression	10 % (78)	10 % (38)	10 % (40)
Missing	0 % (2)	0 % (1)	1 % (4)
Belief in beta-blocker adverse effects*			
Yes	14 % (110)	18 % (72)	9 % (38)
Unsure	61 % (490)	62 % (245)	60 % (245)
No	17 % (133)	11 % (44)	22 % (89)
Missing	8 % (64)	9 % (36)	9 % (37)
Self-reported usage of beta-blockers, FU1*			
Yes	39 % (317)	9 % (34)	69 % (283)
Don't know	5 % (41)	6 % (23)	4 % (18)
No	35 % (281)	65 % (258)	6 % (23)
Missing	21 % (167)	21 % (82)	21 % (85)
Self-reported usage of beta-blockers, FU2*			
Yes	41 % (328)	12 % (48)	68 % (280)
Don't know	5 % (39)	6 % (22)	4 % (17)
No	35 % (286)	65 % (257)	7 % (29)
Missing	19 % (153)	18 % (70)	20 % (83)
CAQ Total, mean (SD)	1.1 (0.6)	1.1 (0.6)	1.1 (0.6)
Missing	6 % (50)	6 % (23)	7 % (27)
CAQ Fear, mean (SD)	1.2 (0.8)	1.3 (0.8)	1.2 (0.7)
CAQ Avoidance, mean (SD)	1.2 (0.8)	1.3 (0.8)	1.2 (0.8)
CAQ Attention, mean (SD)	0.9 (0.6)	0.9 (0.6)	0.8 (0.6)

PCI: Percutaneous Coronary Intervention, CAQ: Cardiac Anxiety Questionnaire.
* $p < .001$.

outcomes, at any of the follow-ups (Table 2, Fig. 2).

2.3. Sensitivity analyses

The complete case analyses yielded no different results than the main analysis (see Appendix Table A2). Similarly, the analyses using self-reported beta-blocker usage as exposure yielded no different results from the main analysis (Appendix Table A3).

2.4. Stratified analyses

No treatment effect was found at any strata at follow-up 1. At follow-up 2, in the strata with moderate baseline CA, randomization to beta-blocker led to a decrease in CA (β = −0.12; 95 % CI: −0.22, −0.02; p = 0.016) (Table 3, Fig. 3).

3. Discussion

In this prespecified substudy of the REDUCE-AMI trial, no significant difference in CA symptoms was observed between patients randomized to beta-blocker therapy and those in the control group who did not receive beta-blockers. This finding was consistent during short- and long-term follow-up, and robust in complete case analysis and self-reported exposure analysis.

To our knowledge, this is the first randomized trial to assess the impact of beta-blockers on CA in patients with preserved cardiac function following AMI. Previous studies have demonstrated that patients with cardiac disease often have an increased awareness of cardiac-related sensations [32], and an increased fear of movement [17], both constituting aspects of CA. Given the anti-anginal properties of beta-blockers and their proven effectiveness in treating somatic symptoms of anxiety it would be reasonable to expect that they also alleviate CA. However, in the present study, no reduction in CA symptoms was observed among patients randomized to beta-blocker therapy, nor among patients taking beta-blockers according to self-reports.

In a post-hoc, exploratory analysis, we stratified patients based on baseline CA levels and assessed the effects of beta-blocker therapy in these subgroups. Interestingly, patients with moderate baseline CA appeared to derive some benefit from long-term beta-blocker treatment, while there was no evidence for an effect for either those with low or high baseline CA. However, these findings should be interpreted with caution due to the exploratory nature of the analysis, and the uneven distribution of patients across groups, with the high-anxiety group being significantly smaller. Despite these limitations, this hypothesis-generating result may warrant further investigation. Possibly, beta-blockers alleviate CA symptoms in patients with moderate baseline CA

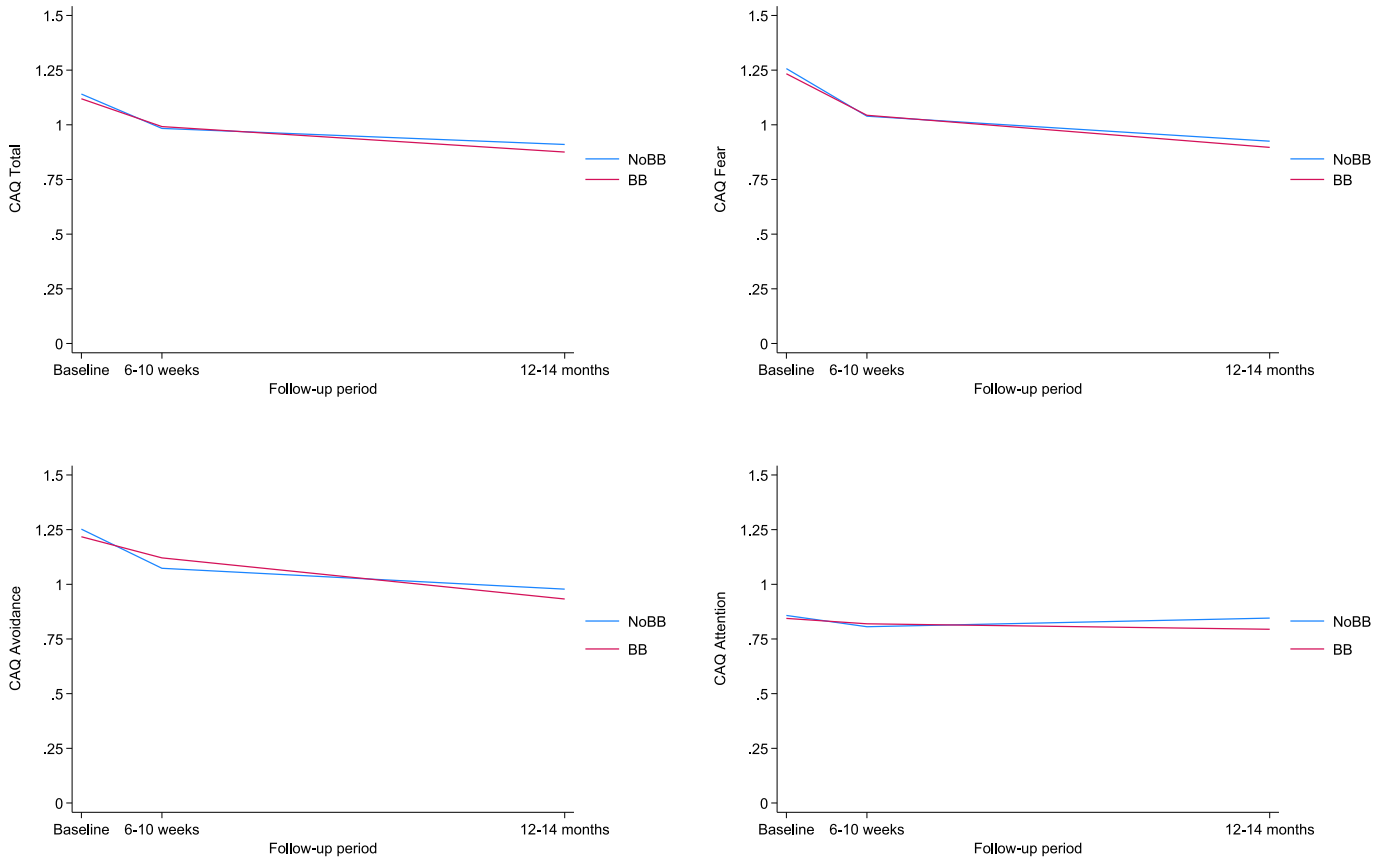

Fig. 2. Panel data of beta-blocker effect for the outcome measures CAQ Total, Fear, Avoidance and Attention at follow-up 1 (6–10 weeks) and follow-up 2 (12–14 months). Note: while the range of the y-axis in this figure is 0–1.5, the true range is 0–4.

Table 2
Regression coefficients, based on randomization to beta-blocker treatment.

	2 months		12 months	
	β (95 % CI)	p-value	β (95 % CI)	p-value
Main analysis (N = 806)				
CAQ Total	0.03 (−0.04, 0.09)	0.398	−0.04 (−0.11, 0.02)	0.168
CAQ Fear	0.03 (−0.06, 0.12)	0.569	−0.03 (−0.12, 0.06)	0.471
CAQ Avoidance	0.03 (−0.07, 0.14)	0.547	−0.06 (−0.16, 0.04)	0.218
CAQ Attention	0.02 (−0.05, 0.09)	0.527	−0.05 (−0.12, 0.03)	0.251

CAQ: Cardiac Anxiety Questionnaire.
Adjusted for age, education, if born in Sweden, sex and baseline assessment of outcome.

Table 3
Regression coefficients, based on randomization to beta-blocker treatment, stratified by baseline CA.

	2 months		12 months	
	β (95 % CI)	p-value	β (95 % CI)	p-value
Sub-group, low CA (*n* = 312)				
CAQ Total	0.02 (−0.07, 0.11)	0.641	−0.05 (−0.14, 0.05)	0.322
Sub-group, moderate CA (*n* = 388)				
CAQ Total	0.02 (−0.07, 0.11)	0.690	−0.12 (−0.22, −0.02)	0.016
Sub-group, high CA (*n* = 56)				
CAQ Total	−0.14 (−0.49, 0.20)	0.416	0.17 (−0.19, 0.54)	0.347

Adjusted for age, education, if born in Sweden, sex and baseline assessment of outcome.
CA: Cardiac anxiety. CAQ: Cardiac anxiety questionnaire. Low CA: CAQ <1, medium CA: CAQ ≥1 & <2, high CA: CAQ ≥2.

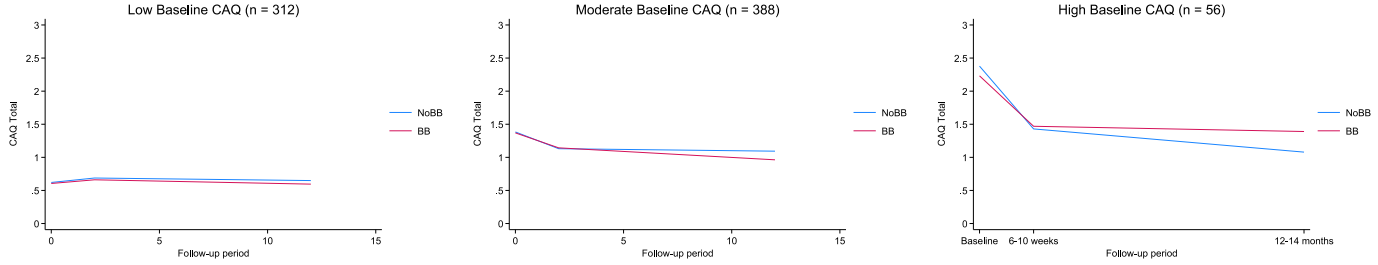

Fig. 3. Panel data of beta-blocker effect for the outcome measures CAQ Total for the subgroups with low, medium and high CAQ at baseline, at follow-up 1 (6–10 weeks) and follow-up 2 (12–14 months). Note: while the range of the y-axis in this figure is 0–3, the true range is 0–4.

levels by making them feel safer, leading to less anxiety in general. It could also be that the previously observed effect of beta-blockers on somatic symptoms of anxiety [33] also apply to CA, and that increased symptoms are required to be able to observe a treatment effect.

3.1. Clinical implications

The result of this substudy suggests that beta-blocker therapy in patients with preserved cardiac function following AMI does not significantly reduce CA. However, it remains possible that certain subgroups of AMI patients are differentially affected, for example as observed here among patients with moderate anxiety at baseline, or in the previous study of long-term vs short-term users of beta-blockers [21]. Although a slightly increased risk for depression has been observed, overall, secondary mental health side effects should not be a pivotal factor in clinical decision making regarding the initiation or continuation of beta-blocker therapy in this patient population. Still, considering the lack of clinical efficacy of routine beta-blocker therapy in this population, individual assessment remains crucial with possibly warranted caution for patients at risk of adverse psychological effects of beta-blocker use.

3.2. Strengths and limitations

As a substudy, this trial did not include all participants randomized in the REDUCE-AMI trial, which makes the study more observational in nature and should be interpreted as such. In general, it consisted of a low-risk population that were well treated with early revascularization and evidence-based secondary preventive treatment at discharge. Moreover, the study population was selected due to logistical reasons (e.g., unavailability of research staff on weekends), which could introduce selection bias and reduce external validity. Nonetheless, baseline characteristics of the treatment groups were well-balanced and comparable to those of the overall REDUCE-AMI population, suggesting that the findings are reasonably representative [34,35]. Additionally, we do not possess information about how complex the PCI was nor about any complication related to the intervention. If this could affect the level of cardiac anxiety is not known.

A major limitation was the open-label design of the main trial. Patients were informed about potential side effects of beta-blockers prior to randomization, and many were aware of their treatment assignment. The absence of a double-blinded, placebo-controlled design may have introduced bias to patient-reported outcomes.

A further limitation is that, similar to many cardiac populations, the patients' average baseline ratings on the CAQ were quite low (≈1) [36,14,37,15]. This may result in a floor effect, where on average it is hard for patients to reduce CA further. This might be a reason why we observed a significant reduction in the post-hoc exploratory analysis.

Finally, conclusions are limited by the large number of missing data on adherence to randomization group. Although less than 10 % reported not being adherent, approximately 25 % of participants did not know or did not report if adherent. This, together with the pragmatic nature of the trial, limits making strict causal inferences about actual beta-blocker medication use. However, based on available data, adherence rates are reasonable (90 %), and the pragmatic design instead allow for inference of real-world effects when prescribing beta-blockers. Additionally, the analysis using self-reported usage of beta-blockers as exposure yielded similar results. However, as it is also limited by missing data on beta-blocker adherence, the analysis carries a high risk of bias and should be interpreted with caution.

4. Conclusion

The evidence of this pragmatic trial suggests that self-reported CA in patients after AMI with preserved cardiac function does not differ between individuals randomized to routine long-term beta-blocker therapy as compared to individuals with no beta-blocker use. While post-hoc analyses suggest that beta-blockers may benefit patients with moderate baseline cardiac anxiety, these results are highly explorative and should be interpreted with caution. Further research is warranted to explore the potential differential effects of beta-blockers across varying levels of cardiac anxiety, using placebo controls and with strict follow-up on adherence.

Funding

This work was supported by grants from the Swedish Heart Lung Foundation (2018:32, 2019:7, 2020:6; 20210216, to Dr. Mars; and 20180187 and 20210273 to Dr. Hofmann), Region Stockholm (2018-0490 and FoUI-974540, to Dr. Hofmann), and the Heart and Lung Association (2018:32, 2019:7, 2020:6 to Dr. Olsson). The U-CARE strategic research environment was funded by The Swedish Research Council (2009–1093).

CRediT authorship contribution statement

Philip Leissner: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Katarina Mars:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Sophia Humphries:** Writing – review & editing, Resources, Investigation, Conceptualization. **Tomas Jernberg:** Writing – review & editing, Project administration, Resources. **Claes Held:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Robin Hofmann:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization, Investigation. **Erik M.G. Olsson:** Writing – review & editing, Supervision, Resources, Methodology, Data curation, Conceptualization, Funding acquisition, Project administration, Software.

Declaration of competing interest

Dr. Hofmann reports lecture fees to institution from AstraZeneca, Pfizer and BMS. Dr. Jernberg reports research grants and consultant fee to institution from MSD and Amgen, respectively.

Acknowledgements

We want to thank the hospital staff at all involved hospitals for recruiting patients and the patients for participating and contributing to research. We also would like to thank U-CARE for assistance with administrative tasks.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2025.02.010.

Data availability

The data underlying this article cannot be shared publicly due to the General Data Protection Regulation (2016/679). The data will be shared on reasonable request to the corresponding author.

References

[1] Wang X, Jiang N, Chen S, Tuerdi S, Yang J, Yan R, He L, Wang J, Li Y. Fear of progression in patients with acute myocardial infarction: a cross-sectional study. BMC Nurs. 2024;23(1):1–12. https://doi.org/10.1186/S12912-024-02552-1/TABLES/8.

[2] Zhen J, Wang J, Wang YL, Jiao J, Li J, Du XJ, Li YL. Fear of recurrence in elderly patients with coronary heart disease: the current situation and influencing factors

according to a questionnaire analysis. BMC Cardiovasc. Disord. 2022;22(1):1–7. https://doi.org/10.1186/S12872-022-02853-W/TABLES/4.
[3] Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, et al. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J 2024; 45(36). https://doi.org/10.1093/EURHEARTJ/EHAE177.
[4] Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001; 357(9266):1385–90. https://doi.org/10.1016/S0140-6736(00)04560-8.
[5] Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44 (38):3720–826. https://doi.org/10.1093/eurheartj/ehad191.
[6] McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368.
[7] Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns HJGM, et al. 2024 ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2024;3314–3414. https://doi.org/10.1093/eurheartj/ehae176.
[8] Grillon C, Cordova J, Morgan CA, Charney DS, Davis M. Effects of the beta-blocker propranolol on cued and contextual fear conditioning in humans. Psychopharmacology 2004;175(3):342–52. https://doi.org/10.1007/s00213-004-1819-5.
[9] Steenen SA, Van Wijk AJ, Van Der Heijden GJMG, Van Westrhenen R, De Lange J, De Jongh A. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. J Psychopharmacol 2016;30(2):128–39. https://doi.org/10.1177/0269881115612236.
[10] Celano CM, Daunis DJ, Lokko HN, Campbell KA, Huffman JC. Anxiety disorders and cardiovascular disease. Curr Psychiatry Rep 2016;18(11). https://doi.org/10.1007/s11920-016-0739-5.
[11] Lian Y, Xiang J, Wang X, Kaminga AC, Chen W, Lai Z, et al. Prevalence of moderate to severe anxiety symptoms among patients with myocardial infarction: a meta-analysis. Psychiatry Q 2021;0123456789. https://doi.org/10.1007/s11126-021-09921-y.
[12] Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. Am Heart J 2015;170(6):1105–15. https://doi.org/10.1016/j.ahj.2015.09.013.
[13] Strik JJMH, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol 2003;42(10):1801–7. https://doi.org/10.1016/j.jacc.2003.07.007.
[14] Leissner P, Held C, Humphries S, Rondung E, Olsson EMG. Association of anxiety and recurrent cardiovascular events: investigating different aspects of anxiety. Eur J Cardiovasc Nurs 2024. https://doi.org/10.1093/EURJCN/ZVAE036.
[15] Van Beek M, Zuidersma M, Lappenschaar M, Pop G, Roest AM, Van Balkom AJLM, et al. Prognostic association of cardiac anxiety with new cardiac events and mortality following myocardial infarction. Br J Psychiatry 2016;209(5):400–6. https://doi.org/10.1192/bjp.bp.115.174870.
[16] Philips HC. Avoidance behaviour and its role in sustaining chronic pain. Behav Res Ther 1987;25(4):273–9. https://doi.org/10.1016/0005-7967(87)90005-2.
[17] Bäck M, Cider Å, Herlitz J, Lundberg M, Jansson B. The impact on kinesiophobia (fear of movement) by clinical variables for patients with coronary artery disease. Int J Cardiol 2013;167(2):391–7. https://doi.org/10.1016/j.ijcard.2011.12.107.
[18] Yndigegn T, Lindahl B, Mars K, Alfredsson J, Benatar J, Brandin L, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024. https://doi.org/10.1056/NEJMOA2401479/SUPPL_FILE/NEJMOA2401479_DATA-SHARING.PDF.
[19] Hjalmarson A, Elmfeldt D, Herlitz J, Holmberg S, Málek I, Nyberg G, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. Lancet (London, England) 1981;2(8251):823–7. https://doi.org/10.1016/s0140-6736(81)91101-6.
[20] Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J 2018;39(42): 3766–76. https://doi.org/10.1093/eurheartj/ehy554.
[21] Leissner P, Mars K, Humphries S, Karlström P, Yndigegn T, Jernberg T, et al. Short- and long-term effects of beta-blockers on symptoms of anxiety and depression in patients with myocardial infarction and preserved left ventricular function: a pre-specified quality of life sub-study from the REDUCE-AMI trial. Eur Heart J Acute Cardiovasc Care 2024;zuae112. https://doi.org/10.1093/ehjacc/zuae112.
[22] Mars K, Humphries S, Leissner P, Jonsson M, Karlström P, Lauermann J, et al. Effects of beta-blockers on quality of life and well-being in patients with myocardial infarction and preserved left ventricular function—a prespecified substudy from REDUCE-AMI. Eur Heart J 2024;1–11. https://doi.org/10.1093/ehjcvp/pvae062.
[23] James S, Rao SV, Granger CB. Registry-based randomized clinical trials – a new clinical trial paradigm. Nat Rev Cardiol 2015;12(5):312–6. https://doi.org/10.1038/NRCARDIO.2015.33.
[24] Yndigegn T, Hofmann R, Jernberg T, Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. Heart 2018;104(19):1562–7. https://doi.org/10.1136/HEARTJNL-2017-312322.
[25] Yndigegn T, Lindahl B, Alfredsson J, Benatar J, Brandin L, Erlinge D, et al. Design and rationale of randomized evaluation of decreased usage of beta-blockers after acute myocardial infarction (REDUCE-AMI). Eur Heart J Cardiovas Pharmacother 2023;9(2):192–7. https://doi.org/10.1093/EHJCVP/PVAC070.
[26] Humphries S, Mars K, Hofmann R, Held C, Olsson EMG. Coronary artery disease randomized evaluation of routine beta-blocker therapy after myocardial infarction quality of life (RQoL): design and rationale of a multicentre, prospective, randomized, open, blinded endpoint study. Eur Heart J Open 2023;3:1–9. https://doi.org/10.1093/ehjopen/oead036.
[27] Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, et al. The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). Heart 2010;96(20):1617–21.
[28] Socialstyrelsen. Registers. Retrieved April 13, 2022, from, https://www.socialstyrelsen.se/en/statistics-and-data/registers/; 2025.
[29] Eifert GH, Thompson RN, Zvolensky MJ, Edwards K, Frazer NL, Haddad JW, et al. The cardiac anxiety questionnaire: development and preliminary validity. Behav Res Ther 2000;38(10):1039–53. https://doi.org/10.1016/S0005-7967(99)00132-1.
[30] Leissner P, Held C, Rondung E, Olsson EMG. The factor structure of the cardiac anxiety questionnaire, and validation in a post-MI population. BMC Med Res Methodol 2022;22(1):338. https://doi.org/10.1186/s12874-022-01820-5.
[31] Plumpton CO, Morris T, Hughes DA, White IR. Multiple imputation of multiple multi-item scales when a full imputation model is infeasible. BMC Res Notes 2016; 9(1). https://doi.org/10.1186/S13104-016-1853-5.
[32] Hohls JK, Beer K, Arolt V, Haverkamp W, Kuhlmann SL, Martus P, et al. Association between heart-focused anxiety, depressive symptoms, health behaviors and healthcare utilization in patients with coronary heart disease. J Psychosom Res 2020;131(October 2019):109958. https://doi.org/10.1016/j.jpsychores.2020.109958.
[33] Hayes PE, Schulz SC. Beta-blockers in anxiety disorders. J Affect Disord 1987;13 (2):119–30. https://doi.org/10.1016/0165-0327(87)90017-6.
[34] Cleland JGF, Mcmurray JJV, Freemantle N. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024;391(1):94–5. https://doi.org/10.1056/nejmc2406095.
[35] Matthews AA, Dahebreh IJ, MacDonald CJ, Lindahl B, Hofmann R, Erlinge D, et al. Prospective benchmarking of an observational analysis in the SWEDEHEART registry against the REDUCE-AMI randomized trial. Eur J Epidemiol 2024;39(4): 349–61. https://doi.org/10.1007/s10654-024-01119-3.
[36] Dragioti E, Vitoratou S, Kaltsouda A, Tsartsalis D, Gouva M. Psychometric properties and factor structure of the Greek version of the cardiac anxiety questionnaire (CAQ). Psychol Rep 2011;109(1):77–92. https://doi.org/10.2466/08.09.15.PR0.109.4.77-92.
[37] Marker CD, Carmin CN, Ownby RL. Cardiac anxiety in people with and without coronary atherosclerosis. Depress Anxiety 2008;25(10):824–31. https://doi.org/10.1002/da.20348.