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PROTOCOL PAPER
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

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Aims

Most cases of acute myocardial infarction (MI) in Sweden are treated with long-term β-blocker therapy as secondary prevention. Case studies and patient reports have indicated negative effects of β-blockers including symptoms of depression, fatigue, sexual dysfunction, and general low mood, all related to reduced quality of life (QoL). To date, no recent large-scale, randomized trial has explored the effects of β-blockers on these factors.

Methods and results

The ongoing Randomized Evaluation of Decreased Usage of beta-bloCkErs after myocardial infarction (REDUCE): quality of life (RQoL) study is a multicentre, prospective, randomized pre-specified substudy aiming to evaluate the effects of β-blockers on self-reported measures of QoL. Following randomized allocation to long-term β-blocker or no β-blocker treatment, patients complete a total of six baseline measures pertaining to QoL, sexual functioning, and perceived side effects. Data collection is optionally carried out online through a unique and secure portal and repeated again at two follow-up time points. Recruitment began in July 2018. Data from the first 100 patients showed that at the first follow-up, 93% had completed the questionnaires, which decreased to 81% at the second follow-up. The method of digital data collection was utilized by over half of the patients recruited so far.

Conclusion

Data from the first 100 patients indicate success in terms of study design and recruitment. The RQoL substudy investigates the effects of β-blockers on self-reported measures of QoL in MI patients and will potentially contribute to the limited knowledge of QoL-related side effects reported in conjunction with β-blocker use.

Clinical trial registration

Eudra CT number, 2017-002336-17; Clinical trial.gov identifier, NCT03278509

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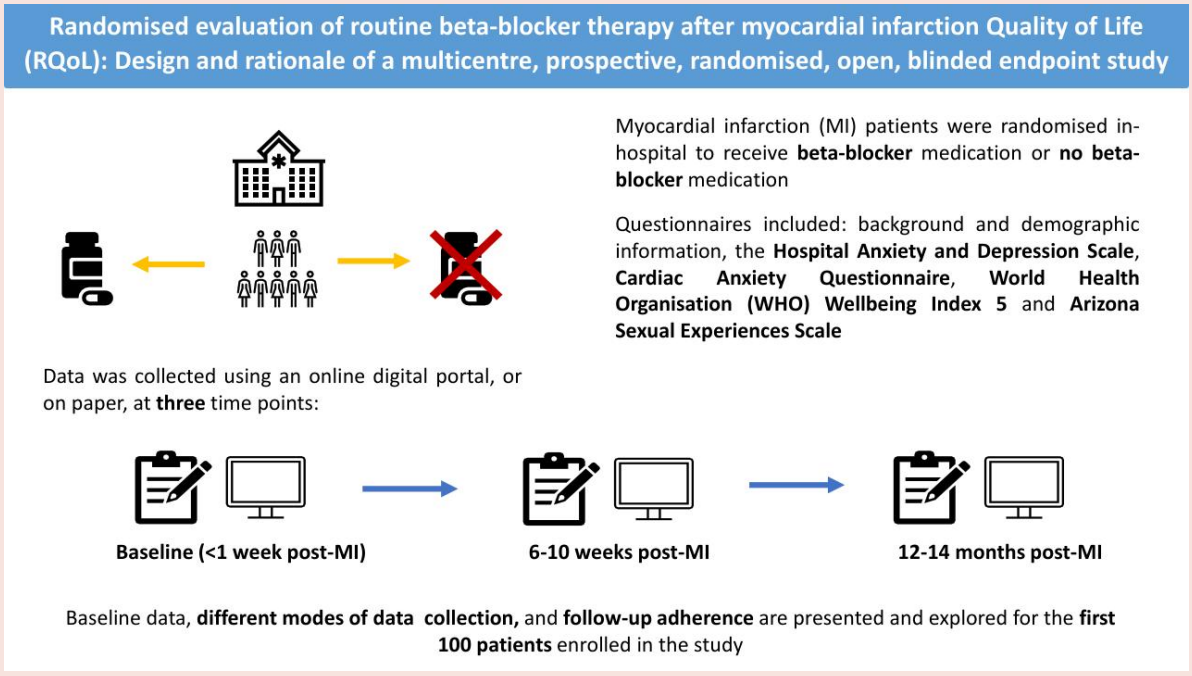
Graphical Abstract



Keywords Adrenergic beta-antagonist • Digital data collection • Myocardial infarction • Nationwide register data • Quality of life • Randomized clinical trial

Introduction

Beta-blockers (β-blockers) have been used for decades to treat patients with acute myocardial infarction (MI) for long-term secondary prevention. This treatment was based on results from early prospective randomized trials that showed long-term treatment improved outcomes and decreased risk for mortality.[1–4] However, these trials were conducted in the 80s, before the introduction of modern treatments, and included patients with reduced left ventricular ejection fraction. In the present day, β-blockers are a cause for controversy within European and international guidelines. Guidelines by the American Heart Association (AHA) are somewhat inexplicit regarding β-blocker use in MI patients with preserved ejection fraction (EF) >40%. Akin to the AHA, the most recent European guidelines by the European Society of Cardiology, recommend β-blocker therapy in higher risk groups, but do not specify long-term treatment in those with preserved EF.[5]

Based on evidence from older studies, most patients with acute MI are treated with β-blockers for secondary prevention upon hospital discharge.[6] And while recent retrospective and register trials have investigated the effectiveness of β-blocker treatment on cardiovascular and mortality outcomes, stating little or no difference in risk between groups,[7–10] there is still a recognized knowledge gap in the area, constituting much need for randomized controlled trials (RCTs). This was the rationale behind the ongoing Randomized Evaluation of Decreased Usage of beta-bloCkErs (REDUCE) trial (ClinicalTrials.gov identifier NCT03278509).

β-Blockers have been implicated as a reason for several patient-reported side effects such as fatigue, hypotension, bronchospasm, bradycardia, reduced libido, and depression. Depending on the severity or intensity of the side effects, it is not unexpected that some patients might feel worse when taking β-blockers, and therefore, a likely reason for subsequent low compliance with the medication after discharge and affecting overall quality of life (QoL).[11] There is no uniform meaning of the term 'quality of life', and its definition and interpretation are often applied differently between various disciplines.[12] The World Health Organization (WHO), however, summed up the consensus among researchers that QoL is: (i) subjective to the individual, (ii) multidimensional (physical, psychological, and social), and (iii) includes both positive and negative dimensions.[13] Moreover, health-related QoL (HQoL) is a concept that refers to health aspects of QoL specifically and the impact of perceived health on the ability to live a meaningful life. In the case of β-blockers, investigation into the association with QoL should ideally cover some, if not all, of these areas.

However, studies exploring the behavioural and psychological aspects of β-blockers particularly on QoL, have been few, and have often indicated conflicting findings. Where some studies have shown an association of β-blockers with depression,[14,15] higher risk for mood disorder–related hospital admissions,[16] fatigue and sexual dysfunction,[17] and impaired incidental learning,[18] other trials have found no association[19,20] or β-blocker superiority compared with no drug treatment or a placebo control.[21,22]

With this conflicting evidence surrounding β-blockers and their association with effects on QoL, *and* a lack of recent RCTs in the area, it is of arguable interest to conduct an RCT to clarify this controversy. This was the authors' rationale behind the REDUCE: QoL (RQoL) study, a pre-specified substudy to the REDUCE trial.[23] To our knowledge, RQoL is the first study to assess the effects of β-blockers

on self-reported measures of depression, anxiety, and QoL as well as sexual functioning in both men and women in a registry-based RCT (RRCT)[24] of patients randomized to β-blocker or no β-blocker treatment. The many strengths of the RRCT design have been addressed and even considered in the context of β-blockers,[25] supporting the suitability for such a study design in this area.

Methods

Study objectives and hypothesis

The present study aims to investigate whether possible differences in terms of cardiovascular outcomes and mortality, as explored in the REDUCE trial,[23] extend to psychologically reported effects and QoL, in patients randomized to β-blocker treatment or no treatment. These reports aim to cover symptoms of anxiety and/or depression, sexual functioning, and overall wellbeing with regard to QoL at short-term (6–10 weeks) and longer term (12–14 months) follow-up, post-MI. The primary outcomes are measurements assessed at 6–10 weeks post-MI and include self-reported symptoms of depression and anxiety, cardiac-focused anxiety, general wellbeing, and sexual functioning. Secondary analysis will explore the same outcomes at a longer follow-up of 12–14 months post-MI.

Study design

The RQoL study is a multicentre, substudy of a prospective, controlled, open-label RRCT. Group allocation is done in the main study (REDUCE; ClinicalTrials.gov identifier NCT03278509)[23] through 1:1 randomization in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[26]

The background and feasibility-related data for the first 100 participants who have passed all three data collection time points will be presented herein.

Inclusion/exclusion criteria

Eligibility for the study was dependent on the patient's eligibility and acceptance into the REDUCE study. Thus, inclusion criteria were as follows: (i) patients ≥18 years, (ii) recruited 1–7 days after MI as defined by the universal definition of MI (Type 1) and included in the SWEDEHEART registry, (iii) undergone coronary angiography during hospitalization, (iv) documented obstructive coronary artery disease by coronary angiography, i.e. stenosis ≥50%, fractional flow reserve ≤0.80 or instantaneous wave-free ratio ≤0.89 in any segment at any time point before randomization, (v) normal EF (≥50%) according to echocardiography performed after MI, and (vi) written informed consent obtained. Further to these criteria, inclusion into the RQoL substudy was dependent on the patient providing additional informed consent and being able to read and understand the Swedish language. Exclusion criteria were: (i) any condition that may influence the ability to comply with the study protocol, (ii) contraindications for β-blockade, or (iii) indication for β-blockade other than as secondary prevention according to the treating physician. *Table 1* shows the baseline characteristics and medical background divided by randomization group.

Informed consent, randomization, and ethics

All patients participating in the RQoL substudy were informed about the study procedures and given the opportunity to decline participation at any point and have their data revoked. Patients who agreed to participate in the study provided written or digital informed consent prior to data collection. This study is protocol version 1.0.0, approved by the Regional Ethical Review Board in Stockholm (dnr 2016/1707-31/4 and 2018/1048-32).

Study procedures

The RQoL study comprises three data collection time points: baseline (in hospital, within 0–7 days following the MI), 6–10 weeks after MI, and 12–14 months after MI.

After randomization to the main REDUCE study, patients were invited to also take part in the RQoL substudy. Those agreeing to participate were subsequently provided with study information and asked to provide consent, either via a secure online portal, the Uppsala University Psychosocial Care Program (U-CARE) Portal (the Portal) or on paper, and in some cases, both. The Portal is specially designed to enable remote delivery of psychological interventions such as those in the U-CARE Heart Trial[27] and is simultaneously used as a method of digital data collection. The design and integrity of the Portal allow for secure collection of data that are later matched, through the personal ID number of the participant, to the unique REDUCE study code thus allowing for easy data retrieval.

Following baseline data collection, hospital staff regularly send a separate study log of all patients entered in the study to the researchers at Uppsala University who are responsible for the rest of the patient contact from this point forward and at the other study follow-up time points. These researchers register patients on the logs received from each hospital into a combined study log which sometimes includes entering the patient's answers into the Portal manually.

Six to 10 weeks following the MI and the baseline measures, patients were automatically informed that the next observation point had opened and that it was time to fill in the first set of follow-up questionnaires. These questionnaires contained the same measures as those given at baseline, with the addition of new questions pertaining to whether the patient was taking β-blockers and, if so, whether they had experienced any side effects. Patients were given 4 weeks to respond. This process was completed in the same manner at both follow-ups, with an additional 4 weeks to respond to the last (12–14 months) follow-up.

Digital data collection

Data were collected primarily through the Portal. In order to be entered into the Portal, participants must have a Swedish personal ID number. It is also possible to login with BankID, a fast digital identification service that allows for user authentication connected to the individual's personal ID number and a bank account. Users added to the Portal without a BankID did so with an email address and password and were sent a double-authentication code though short message service (SMS) to log in.

Upon the study observation points opening at 2- and 12-month follow-ups, participants were automatically sent SMS and email notifications with the study page and login information. After 1 week, unresponsive participants received automatic email and SMS reminders. If, after a further 1 week, the participant had still not filled in the questionnaires, the participant was contacted by phone by the responsible researcher. Those with paper questionnaires were instead sent out the forms with a pre-paid return envelope and an instructional letter and were reminded in the same way by telephone after 2 weeks. Paper questionnaire responses were manually entered into the Portal by research staff so that all data was available via the Portal regardless of response mode.

Outcomes

The primary outcomes are self-reported symptoms of depression and anxiety, including cardiac-focused anxiety, general wellbeing and sexual functioning measured 6–10 weeks post-MI. Secondary analysis will focus on the same outcome measures at 12–14 months post-MI.

Demographic and background information were collected from the patient registries, the study log filled in by staff on-site at each hospital, and a short questionnaire included at the beginning of each data collection point.

(1) Depression and anxiety were measured according to the Hospital Anxiety and Depression Scale (HADS)[28] which consists of 14 items ranked 0–4 and which when added together compute the HADS total score (HADS-T). Seven of the items pertain to the depression subscale (HADS-D) and the other 7 to the anxiety subscale (HADS-A). A HADS total score of >7 indicates borderline abnormal levels of depressive and/or anxiety symptoms.
(2) Heart-focused anxiety was measured by the 18-item Cardiac Anxiety Questionnaire (CAQ)[29] which ranks responses on a 0–4 scale of self-rated frequency of experiencing the behaviour. The total CAQ score (0–72) can be calculated by adding each individual response, with higher scores indicating greater heart-focused anxiety.[29]

Table 1 Baseline medical characteristics of the first 100 patients with acute myocardial infarction participating in the RQoL study

Randomization group	Total, *N* 100	β-Blocker, *N* (%) 45	No β-blocker, *N* (%) 55	Missing data (*N*)
Sex				
Male	80	35 (78)	45 (82)	
Female	20	10 (22)	10 (18)	
Mean age (years)	64.4	65.1	63.9	
Marital status				**1**
Single	**19**	**7**	**12**	
Married or living with partner	**71**	**34**	**37**	
Living apart	**8**	**4**	**4**	
Other	**1**	**0**	**1**	
Country of birth				**1**
Sweden	**84**	**36**	**48**	
Outside Sweden	**15**	**9**	**6**	
Education level				**2**
Primary	**24**	**9 (9.2)**	**15 (15.3)**	
Secondary	**33**	**13 (13.3)**	**20 (20.4)**	
University ≤3 years	**19**	**11 (11.2)**	**8 (8.2)**	
University >3 years	**22**	**12 (12.2)**	**10 (10.2)**	
Smoking status				
Never smoked	52	29 (29)	23 (23)	
Ex-smoker	30	8 (8)	22 (22)	
Smoker	18	8 (8)	10 (10)	
Medical history				2
Previous MI	9	5 (11)	4 (7.3)	
Diabetes mellitus	11	6 (13.3)	5 (9.1)	
Hypertension	49	23 (53.4)	26 (47.3)	
Previous stroke	3	1 (2.2)	2 (3.6)	
Previous PCI	9	4 (8.9)	5 (9.1)	
Psychological treatment				
Psychiatric medication	7	3 (6.7)	4 (7.3)	
Procedures during hospitalization				2
PCI	96	41 (95)	55 (100)	
CABG	2	2 (4.4)	0 (0)	

Medical data were provided by SWEDEHEART.
ACE inhibitors, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STEMI, ST-elevated myocardial infarction; SWEDEHEART, Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies register.

(3) The WHO's wellbeing index (WHO-5)[30] is a five-item self-reported index of current wellbeing included in the outcome measures. The total score ranges from 0 to 25 and is multiplied by 4 to give the final score, with 0 representing the worst possible well-being imaginable and 100 the best.
(4) The Arizona Sexual Experiences Scale (ASEX)[31] collects data on patients' recent sexual activity and perceived level of enjoyment/difficulty regarding this and is scored from 1 to 6. Item scores are added together to make a total score (5–30). A total score of >19, scoring 5 or more on any item or scoring 4 or more on 3 items indicates sexual dysfunction.

Health-related QoL was measured with the EQ-5D[32] which is collected routinely within the national register including all participants in the REDUCE main study. It is a standardized questionnaire containing five question items covering different domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each item is scored across three response levels (1 = 'no problems', 2 = 'some problems', 3 = 'extreme problems'). This is followed by the second part of the EQ5D, the visual analogue scale, a scale from 0 to 100 of self-rated health status. The EQ-5D is administered to all patients in the Secondary prevention after Heart Intensive Care Admission (SEPHIA) register at both routine follow-up occurrences (6–10 weeks and 12–14 months post-MI). As this is a national register, coverage is wide, although the exclusion criteria >75 years, which were recently changed to >80 years in 2018, mean not all patients are included in this part of the register.

Patients were also asked about their expectations of the side effects from taking β-blockers and their attitudes towards taking medication in general, measured using a version of the Beliefs about Medicines Questionnaire[33] at the end of the first data collection point. As this was an open-label study, expectations might influence the experience and attribution of psychological side effects. Measuring expectations at baseline was an attempt to control for this variable.

At the first and second follow-ups, the patients answered a question pertaining to whether they were taking β-blockers and, if so, whether they experienced any side effects of the medication and to what extent. This was asked using an open format and to determine if any group cross-over had taken place. These questions were added retrospectively to the digital and paper questionnaires, ~6 months after recruitment had started and are therefore missing data for some patients at baseline and first follow-up.

Statistical considerations

There are four separate and equally important primary outcome domains: (i) symptoms of depression, (ii) symptoms of anxiety (including heart focused anxiety), (iii) self-rated general wellbeing and QoL and lastly, (iv) sexual functioning and enjoyment.

Data will be analysed according to the intention to treat principle based on the randomization group and utilizing multiple imputation of missing data. Linear regression will be applied with the follow-up measures as outcomes and controlling for baseline levels as covariates. For precision, age and sex will also be entered in the main models. Sensitivity analyses will investigate if the results hold for complete cases and per-protocol treatment (based on self-reported β-blocker usage). The effect of medical history, sociodemographic characteristics, previous experience of β-blocker, previous psychiatric medication use, and expectations and attitudes of pharmacological treatments on the results will also be explored.

A moderate-to-small effect size of 0.25 standardized mean difference can be detected with a sample size of 251 participants in each group, for a total of 502. We plan to recruit at least 600 participants, allowing for 16% attrition of complete cases. Recruitment will continue until 2022.

Study sites and recruitment RQoL began recruitment in July 2018 at two hospitals in Sweden. At present, nine Swedish hospitals are RQoL study sites, and recruitment is currently ongoing. Baseline data presented in the current paper were collected mostly in-hospital, within 7 days of the MI date. Follow-up data points at 6–10 weeks and 12–14 months post-MI were completed by the patient remotely.

Results

The first 100 patients, recruited from 4 Swedish hospitals took ~10 months to recruit. Between July 2018 and June 2022, 811 patients were recruited into the study. Data from the first 100 recruited patients in the study showed that 93% (93 out of 100) and 81% (80 out of 99) filled in the 6–10 weeks and 12- to 14-month questionnaires, respectively. One patient died before the second follow-up. The flow of patients included in the study is shown in *Figure 1*. *Table 1* reveals that 80% of the patients were males, with a mean age of 64.4 years. Most of the background data for variables presented in *Table 1* reveal the two treatment groups to be well balanced after randomization. *Table 2* shows additional background demographic data as well as mean scores for the HADS, CAQ, WHO-5, and ASEX measures at baseline, which appear to be well matched between groups. Missing data, time to respond, response format, and reminders at baseline, first follow-up, and second follow-up are also displayed in *Table 2*. Of those reminded, the better response rate was in the first follow-up where only 4 out of 29 reminded patients did not complete the questionnaires. This increased to 10 out of 30 with the second follow-up.

Discussion

The purpose of the RQoL substudy is to collect data from recent MI patients with normal EF on multiple measures of QoL, including mental health and sexual dysfunction, to evaluate whether there is a difference between those treated or not treated with β-blocker medication. This report summarizes the design and methodology of the study, the study procedures, and the baseline characteristics of the first 100 patients recruited into the study and has indicated that the method of recruiting patients in hospital, directly from the main REDUCE trial, has been successful.

Recruitment into the study was feasible and participant retention at both follow-up time points was good. Nearly all patients had completed the first follow-up (93%) and the majority (81%) had completed the second follow-up at 12–14 months post-MI. With the current recruitment pace and another year of recruitment planned, the sample size should be adequate to reach a sufficient power level.

In general, digital data collection methods are considered an advantage and this study tried to utilize them as much as possible, for example by allowing for digital consent to be provided through the use of BankID. In Sweden, 94.8, 83.3, and 66.4% of those aged 51–60, 61–70, and 71–80 years have BankID, respectively,[34] and while these data would therefore indicate that the majority of our sample presented have access to BankID, the proportion of those completing on paper was higher than this. Therefore, the advantages and disadvantages of using the internet or digital devices should be considered in this context. While the research team had initially planned that the data collection was mostly undertaken in digital format through the Portal, 48 out of the 98 patients who completed the baseline measures did so on paper. This number decreased at both follow-ups with ~40% of questionnaires completed on paper vs. the original 49% at baseline. This number, while not a large decrease, is indicative that some patients using paper forms at baseline switch to digital methods at follow-ups, thus decreasing the time and resources required for paper methods by research staff. It was likely that staff availability or a short time to discharge may have contributed to the data collection on paper in these cases. Technical difficulties and teething problems that have been encountered in the early stages of the trial have largely been resolved, but staff shortages meant that some patients were unable to be offered the digital data collection option, or in some cases, unable to be asked about participation in RQoL at all. It should also be considered that while the justification for including two methods of data collection was to increase accessibility options for patients, there is a risk for potential selection bias in using different data reporting methods. This can be investigated by comparing the treatment groups by data collection method (digital vs. paper) but remains a methodological limitation to consider when interpreting future results.

Of note, data from the first 100 patients show a rather high proportion of males compared with female patients. However, this is not entirely unexpected for the mean age (64.4 years) of the sample. In the INTERHEART case–control study, it was shown that women experience their first MI on average 9 years later in life than men[35] which might explain the relatively higher proportion of male patients in the sample. Moreover, this overrepresentation of men in studies of MI or treatment of MI means that most questions pertaining to sexual dysfunction have focused on impotence or erectile dysfunction, thus women have often been overlooked in the reporting of side effects of β-blockers in this area. Most studies that have investigated sexual dysfunction have done so with male patients only.[17,36] The RQoL study, by using the ASEX questionnaire that is aimed at both men and women, has the advantage of collecting data from both perspectives.

Research with strong evidence for the link between psychological and cardiovascular health supports the importance of acknowledging this relationship,[37–39] and therefore, the need to monitor the overall wellbeing and QoL of patients with cardiovascular disease.[40] In this study, the authors measured baseline levels of HADS depression and anxiety across both groups. While these outcomes have been previously reported in a study of the Swedish general population,[41] no previous data from patients after MI exists. It would not be unexpected for baseline levels to be higher among cardiac patients than among the general population. Experiencing symptoms of emotional distress is a common finding after MI, with a reported 38% doing so at 2 months post-MI, decreasing only to 30% 12 months after MI.[37] CAQ scores among cardiac patients have also been found to be higher when compared with other patient groups with non-cardiac-related chronic illnesses.[42] Although we are unable to draw any conclusions from the baseline scores of

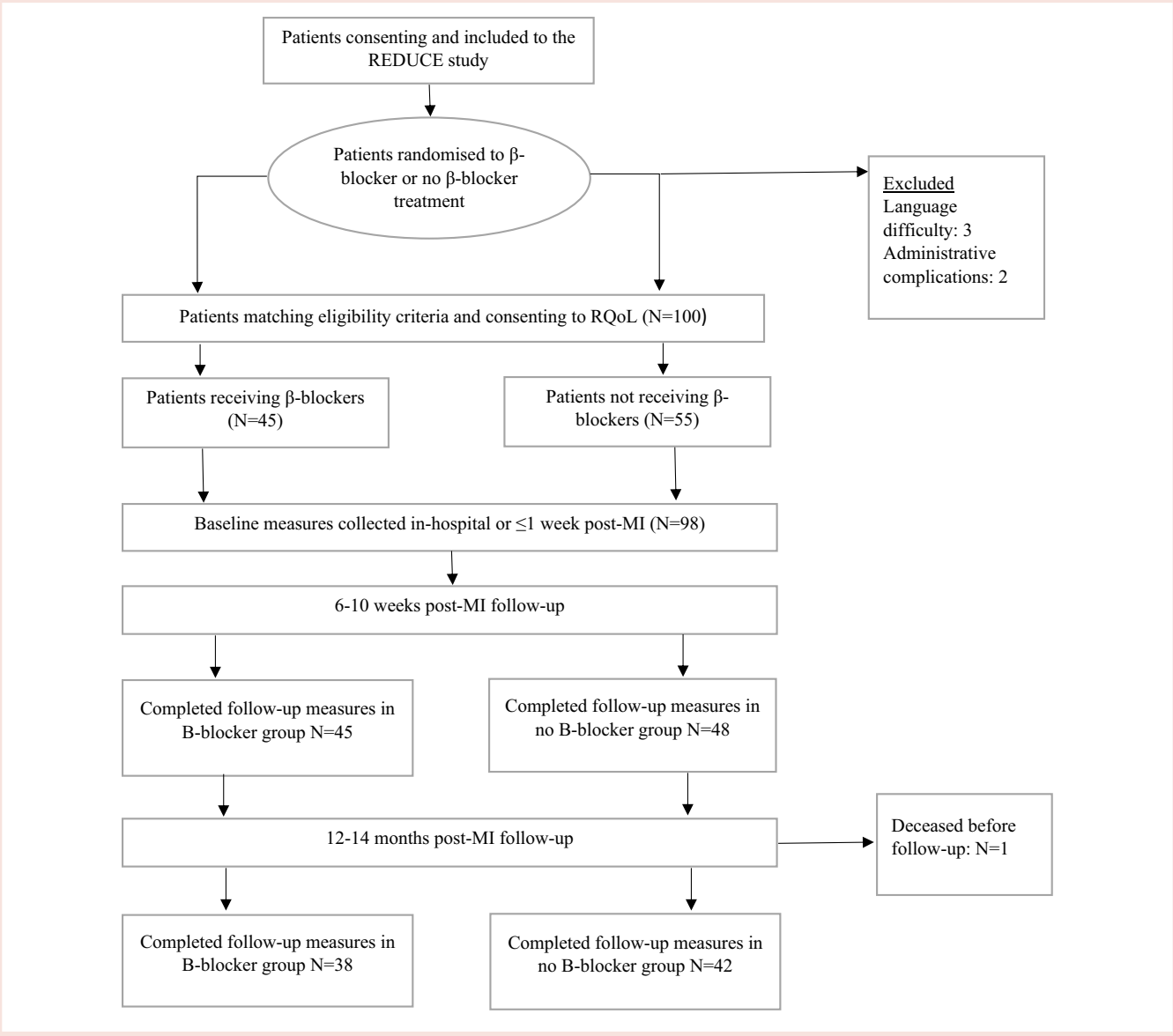


Figure 1 Flow chart of the first 100 patients recruited and followed up across two time points.

this relatively small sample of patients, the treatment groups appear to be evenly matched in most baseline measures, exhibiting an important element of the randomization process and a positive inclination towards the feasibility of the trial.

A large part of this study included administrative co-ordination and patient telephone contact. In general, the number of patients needing telephone reminders was medium level, with around a third at both follow-ups receiving at least one phone call. The total reminded includes all patients who were contacted by phone, including those who did not answer. Therefore, a likely portion of the 10 patients were never actually reached at all or were unavailable at the time of the calls. In all, the majority of those that were reminded through telephone calls completed the follow-up questionnaires upon receiving the reminder. This indicates that although it is a more time-consuming method, it yielded generally good results as a method of minimizing the total number of lost follow-up cases.

One disadvantage of the study in general is the potential for group crossover. Although we tried to control as much as possible for crossover indication, by collecting data from patients regarding β-blocker use, this is still a factor the present study will need to consider. We identified cases in which the reported treatment was different at follow-up from that of the treatment the patient was discharged with, indicating a group crossover. This information was taken from the self-reported answer to whether the patient was currently receiving treatment in the form of β-blockade and compared with their group allocation in the REDUCE trial. The number of crossovers for those in the β-blocker treatment group may even be higher, however, with one study reporting that only 45% of MI survivors were adherent to β-blockers (i.e. did not stop treatment) after 1 year from hospital discharge as measured by 'covered days' from collection of their prescription.[43] The planned analyses will try to control for this crossover and will utilize data from the national Prescribed Drug Registry at the end of the trial to address this issue, but this problem will still need to be considered when drawing any conclusions from the data.

The open-label randomization is a further limitation in this study design. Since this is one of the first RCTs investigating the effect of

Table 2 Background demographic information of the first 100 patients participated into the RQoL study, divided by treatment group

	Total, *N*	β-Blocker, *N* (%)	No β-blocker, *N* (%)	Missing data, *N*
Randomization group	100	45	55	
Baseline				2
Digital format	50 (51)	24 (24.5)	26 (26.5)	
Paper format	48 (49)	21 (21.4)	27 (27.6)	
Mean days between MI and baseline	1.6 days	1.8 days	1.4 days	
Min and max days between MI and baseline	0–7 days	0–6 days	0–7 days	
HADS anxiety scale	5.9	6.5	5.4	2
HADS depression scale	3.8	3.8	3.8	3
CAQ total score	20.7	19.6	21.7	8
WHO-5 total score	62.2	63.2	61.3	2
ASEX total score[a]	10.9	11.4	10.7	7
Follow-up 1				
Total number responding	93	45	48	
Digital format	56 (60)	29 (31)	27 (29)	
Paper format	37 (40)	16 (17)	21 (23)	
Number reminded (of which responded)	25 (27)	8 (9)	17 (19)	
Number reminded (total)	29 (30)	8 (9)	21 (23)	
Not responded	3	0 (0)	3 (3)	
Declined further participation	4 (4)	0 (0)	4 (4)	
Mean days between prompt and OP completion	6.7 days	5.7 days	7.7 days	
Minimum number of days	0	0	0	
Maximum number of days	30	23	30	
Follow-up 2				
Number responding (total)	80 (81)	38 (40)	42 (44)	
Digital format	49 (61)	26 (32.5)	23 (28.5)	
Paper format	31 (39)	12 (15)	19 (24)	
Number reminded (of which responded)	20 (25)	9 (11)	11 (14)	
Number reminded (total)	30 (31.6)	13 (13.7)	17 (17.9)	
Not responded	13 (13.7)	6 (6.3)	7 (7.4)	
Declined participation	2 (2)	0 (0)	2 (2)	
Deceased	1 (1)	1 (1)	0 (0)	
Mean days between prompt and OP completion	6	5.3	6.5	
Minimum number of days	0	0	0	
Maximum number of days	28	19	28	

ASEX, Arizona Sexual Experiences Scale; CAQ, Cardiac Anxiety Questionnaire; HADS, Hospital Anxiety and Depression Scale; WHO-5, World Health Organization Wellbeing 5 Scale.
[a]Items 1–3.

β-blockers on QoL, we cannot rule out the potential contribution of nocebo and drucebo effects on consequent self-reported side effects such as demonstrated in open-label treatment with statins.[44,45] Until further studies have investigated these potential effects in β-blockers, interpretation of the upcoming results should be made with this in mind.

Conclusion

The RQoL substudy investigates the potential self-reported effects of β-blockers vs. no β-blockers on factors related to QoL in patients following MI with normal left ventricular function and will potentially contribute to fill the current void from lacking RCTs in this area. Data collection is made largely using an internet portal and demonstrates the benefits of digital data collection both in and out of the hospital setting.

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Conflict of interest: No relationship with industry or conflict of interest relevant for this trial were reported.

Data availability

The data underlying this article were collected via the U-CARE portal and supplemented by data provided by the SWEDEHEART registry. Data will be provided upon request to the corresponding author with permission from these parties and the ethical authority.

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