Association between β-blocker dose and quality of life after myocardial infarction: a real-world Swedish register-linked study

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Background	β-blockers are routinely administered to patients following myocardial infarction (MI), yet their potential effect on health-related quality of life (HRQoL) is not entirely understood. We investigated the relationship between two different doses of β-blockers with HRQoL following MI.
Methods and results	This nationwide observational study used Swedish national registries to collate sociodemographic, clinical, medication, and HRQoL {the latter operationalized using EuroQol [European Quality of Life Five Dimensions Questionnaire (EQ-5D)]}. Estimates at 6–10 weeks and 12–14 months post-MI follow-up from pooled linear and logistic models were calculated after multiple imputation. We identified 35 612 patients with first-time MI, discharged with β-blockers, and enrolled in cardiac rehabilitation between 2006 and 2015. Upon discharge, patients were either dispensed <50% [24 082 (67.6%)] or ≥50% [11 530 (32.4%)] of the target dosage, as defined in previous trials. After adjusting for pre-defined covariates, neither the EQ-5D Index nor the Emotional Distress items were statistically different between groups. The EQ-VAS score was significantly lower in patients treated with ≥50% target β-blocker dose than those treated with <50% of the target dose [−0.87 [−1.23, −0.46], $P < .001$]. Results were similar at the 12-month follow-up and across sub-groups separated by sex and age.
Conclusion	No difference in HRQoL was found among patients taking <50% vs. ≥50% of the target β-blocker dose, except for the EQ-VAS in which higher scores were reported in those taking a lower dose. The clinical meaningfulness of this statistical significance is likely low.

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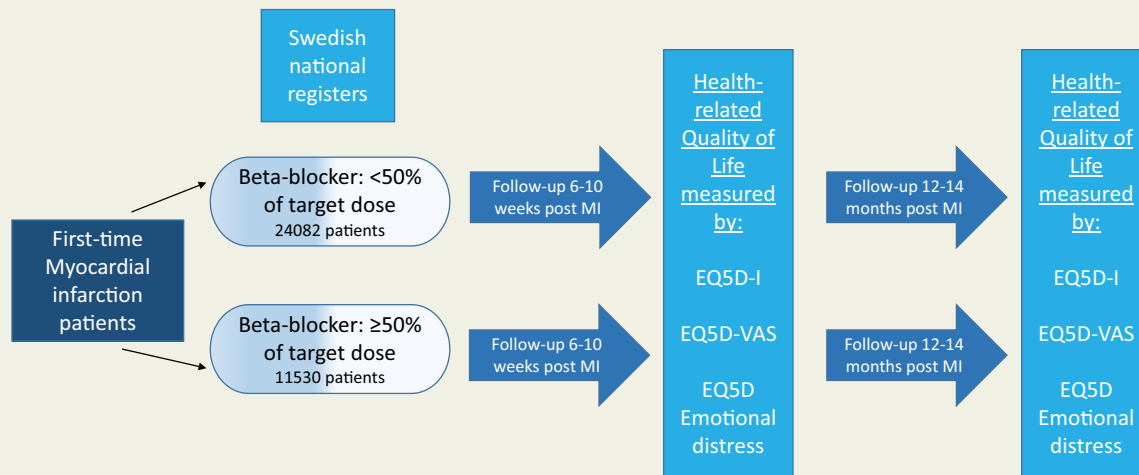† S.H. and J.W contributed equally.

Graphical Abstract

Association between β-blocker dose and quality of life after myocardial infarction
A real-world SWEDEHEART-linked register study

Swedish national registers

First-time Myocardial infarction patients

Beta-blocker: <50% of target dose
24082 patients

Beta-blocker: ≥50% of target dose
11530 patients

Follow-up 6–10 weeks post MI

Follow-up 6–10 weeks post MI

Health-related Quality of Life measured by:

EQ5D-I

EQ5D-VAS

EQ5D Emotional distress

Follow-up 12–14 months post MI

Follow-up 12–14 months post MI

Health-related Quality of Life measured by:

EQ5D-I

EQ5D-VAS

EQ5D Emotional distress

First time post-myocardial infarction patients taking <50% or ≥50% of the recommended β-blocker dose were followed through the Swedish register to investigate whether differences existed between the groups in regards to self-reported health-related quality of life.

Introduction

β-blocker therapy is routine treatment for most patients after acute myocardial infarction (MI) and has been the standard practice for decades.

Side-effects of β-blocker medication such as hypotension, fatigue, and bradycardia are typically acknowledged,[1] while the association between β-blocker use and the effects on patient-reported health-related quality of life (HRQoL) is less established. β-blockers have for example been linked to factors known to have a negative impact on HRQoL such as symptoms of depression, an increased prescription of anti-depressive medication,[2] and sexual dysfunction.[3] Yet, other trials have found no association between β-blocker use and depression or sexual functioning.[4,5]

To date, evidence is largely inconsistent. Some studies suggest a negative association between β-blocker medication, including different dose effects, and HRQoL, while others have found no or even positive associations with β-blocker medication.[6,7] Since there are many disparities in the literature, and since throughout Europe it is current practice that the majority of patients are treated with β-blockers following MI,[8] comparing doses of β-blocker and their association with HRQoL could be key in understanding present knowledge inconsistencies in the field.

Few studies, if any, have investigated β-blocker dose relative to HRQoL,[4] but studies have begun to utilize national registries, where vast amounts of prescription and health data availability have made it possible to conduct large-scale observational studies investigating the association between β-blocker dose and cardiovascular outcomes.

Such registry-based studies reported that treatment with a higher dose of β-blockers (≥50% of the target dose) was not negatively associated with mortality and cardiovascular outcomes compared with treatment with a lower dose of β-blocker (<50% of the target dose) or even no β-blocker treatment.[9,10] Yet, registry studies have thus far not investigated whether a dose-dependent relationship of β-blockers is associated with HRQoL.

The European Quality of Life Five Dimensions Questionnaire (EQ-5D)[11] was created to measure HRQoL. The EQ-5D has been used extensively in cardiovascular (CV) disease-related research and, although somewhat crude, has shown good evidence of reliability and validity as well as ease of use, supporting its widespread clinical application.[12] Registry studies have utilized the EQ-5D outcome to investigate HRQoL in patients with CV diagnoses including MI[13–15]; however, none have explored the role of β-blocker dose on HRQoL with the EQ-5D following MI in a nationwide registry study.

With the present lack of studies investigating the association between β-blocker dose and HRQoL after MI, we decided to conduct an observational cohort study using Swedish national registers to investigate the association between β-blocker dose and HRQoL measured at two time points, in first-time MI patients.

Methods

Registries and data
The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated Accorded to

Recommended Therapies (SWEDEHEART) registry[16] was utilized in the present study. SWEDEHEART registers >100 variables related to hospital admissions for acute coronary syndrome (including date, time, site variables, MI diagnosis, medication history, comorbid conditions, demography) at all coronary care units (CCUs) in Sweden. Diagnoses were taken from the 10th International Classification of Diseases system (ICD-10). A diagnosis of MI (ICD-10, I21-I23) according to current guidelines was decided by the on-site cardiologist, independent of the present study. SWEDEHEART has excellent nationwide coverage (>90% of MI patients <80 years, 100% of the CCUs).

All admissions and outpatient visits to specialists in Sweden, including dates, treatments, and diagnoses, are registered in the National Patient Registry (NPR).[17] All dispensed drugs from pharmacies are registered by the national Prescribed Drug Registry (PDR) which includes variables such as medication type, dose, prescription date, and dispensing date. The national quality health registers comprise unselected clinical population registers and hold the aim to capture all Swedish cases of the condition/disease in question. The NPR and PDR are managed by the National Board of Health and Welfare in Sweden (NBHWS; Socialstyrelsen).

Statistics Sweden (SCB), the national agency in charge of official statistics, annually registers repeated measurements on several socioeconomic variables of interest (e.g. country of birth, income, and education).[18]

When a patient with a first-time MI is registered in SWEDEHEARTs Register of Information and Knowledge about Swedish Heart Intensive Care Admissions, a CR follow-up is automatically generated in the sub-registry for Secondary Prevention after Heart Intensive Care Admission (SEPHIA). In the SEPHIA registry, patients below 75 years were followed the first year post-MI, capturing between 75 and 80% of those eligible. Follow-up takes place at two time points; 6–10 weeks and 12–14 months after MI. Exclusion criterion was age 75 years or above. SEPHIA collects data on secondary prevention variables, including HRQoL as measured by the EQ-5D 3-level version (EQ-5D-3L). The EQ-5D-3L is a standardized questionnaire with five questionnaire items covering different domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and offers a three-level response to each questionnaire item i.e. 1 = 'no problems', 2 = 'some problems', and 3 = 'extreme problems' corresponding to the self-assessed degree of problems per each domain. To obtain a dichotomized variable for Emotional distress, the EQ-5D anxiety/depression questionnaire item can be separated into two levels from the three possible response levels (1 = no emotional distress, 2 or 3 = emotional distress). The Visual Analogue Scale (VAS) is the second part of the EQ-5D questionnaire in which patients mark their self-perceived current health status from 0 to 100 (where 0 = the worst imaginable health state and 100 = the best). The EQ-5D index score is the converted single weighted index score based on the entire questionnaire. This index score was based on the British population norm (range −0.22 to 1.00) which is applicable to the Swedish setting.[19] The EQ-5D has the benefit of its versatility to be applied across multiple settings and countries.

Data identification and ethics
SWEDEHEART data was linked to the PDR, NPR and data from SCB by each patient's unique personal identification number. The identifier key is saved by the NBHWS and only pseudonymized data was provided to the researchers. Thereafter data processing and analysis was performed.

Patients hold the right to deny that their details be added to the SWEDEHEART registry as well as the right to withdraw their details at any time from the registry without cause. They are informed of this opt-out procedure (i.e. waived consent) as well as who will be able to access the data and how the data will be used. The data underlying this article cannot be shared publicly due to legal reasons. The present study was approved by the Regional Ethical Review Board in Uppsala, Sweden (2013/478) and adheres to the Declaration of Helsinki.

Study population
Figure 1 details the flow of patients through the study. In total, 129 913 unique patients admitted with a first-time MI were registered in SWEDEHEART from 1 January 2006 to 31 December 2015.

Exposures
β-blocker dose was the main exposure and was obtained from the first dispensation post-discharge. In agreement with prior studies,[20–23] target doses of prescribed β-blockers were as follows: metoprolol 200 mg/day; bisoprolol 10 mg/day; atenolol 100 mg/day. β-blocker dose was dichotomized into two groups based on the proportion of the pre-defined target dose as defined in previous trials[1,20,23] : <50% of the target dose (reference dose) and ≥50% of the target dose. All dosages assumed a patient consumption of one pill per day. Reference dosage was the same across all analyses (<50%).

Analyses
Main analysis was conducted on the full cohort of patients with first-time MI patients aged 18–74 years, registered in SWEDEHEART who survived until the second SEPHIA follow-up, and enrolled in cardiac rehabilitation.
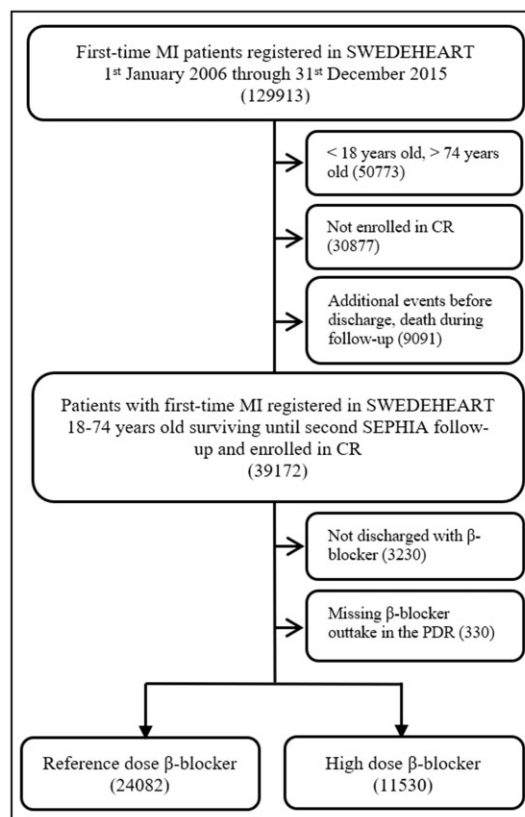

Figure 1 Study flowchart. CR, cardiac rehabilitation; PDR, Prescribed Drug Registry; SEPHIA, Secondary Prevention after Heart Intensive care Admission registry; SWEDEHEART, Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies.

Secondary sensitivity analyses were performed (i) in pre-defined subpopulation strata by sex (male/female) and age (<65 years/65–74 years), (ii) as a complete case analysis, and (iii) through selecting the second β-blocker dispensation as alternative outcome and repeating all analyses to ascertain dosage stability (exposure misclassification).

Outcomes

Primary outcome was EQ-5D index score (EQ5D-I). Secondary outcomes were (i) EQ-VAS and (ii) Emotional distress based on the EQ-5D-3L anxiety/depression questionnaire item. Outcomes were analysed at both SEPHIA time points at 6–10 weeks and 12–14 months post-MI, respectively.

Covariates

Covariates were included based on a directed acyclic graph aimed at control for measured confounding and to increase the precision of estimated associations. In-hospital variables included the following: hospital size (tertiles: small/medium/large), admission year, admission-to-discharge time (hospital stay), sex, age, smoking status (never/former/current smoker), occupational status (working, sick-leave, unemployed/retired/student or other), diabetes, body mass index (BMI), hypertension, previous stroke, left ventricular ejection fraction (LVEF), heart rate, systolic blood pressure (SBP), infarction type ST segment elevation myocardial infarction/non-ST segment elevation myocardial infarction (STEMI/NSTEMI), reperfusion and revascularization. Discharge medications were angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), oral anticoagulation, other antiplatelets, aspirin, calcium channel blockers (CCBs), digitalis, diuretics, statins, other lipid lowering agents, nitrates. Prior diagnosis of asthma, bronchitis, emphysema, other chronic respiratory disease, peripheral artery disease, depression, and anxiety were also included as covariates in the model. Socioeconomic status (SES) variables were country of birth (foreign/Sweden), prior year household income adjusted for family composition (quintiles), and highest attained education (primary/secondary/higher).

Statistics

In summary, numerical variables are descriptively presented as either their arithmetic mean (SD), or median [interquartile range], and categorical variables as count (%) unless otherwise specified. Multiple imputation via chained equations and predictive mean matching was performed to handle missing data. Pooled analyses across the five imputed datasets followed Rubin's rules.[24,25] Variables with most missing data were STEMI/NSTEMI infarct type (19.1%), LVEF (14.2%), EQ5D-I at second follow-up (14.1%), physical activity at second follow up (13.9%), EQ5D-VAS at second follow-up (13.9%), and emotional distress at second follow-up (13.8%).

Crude and adjusted linear (for outcomes EQ5D-I, EQ5D-VAS) and logistic (for outcome emotional distress) regression was applied to estimate pooled point estimates with cluster robust 95% confidence intervals (CIs). Models included linear main effects with age also modelled as a quadratic term. For stratified analyses, the variable stratified on was not adjusted for with the exception of numerical age which still had to be adjusted for within each age strata.

Data pre-processing and analysis was performed in R version 4.0.1.[26]

Results

The total study population included 35 612 unique patients with first-time MI aged between 18 and 75 years, discharged with β-blocker whom survived until the second SEPHIA follow-up and were enrolled in cardiac rehabilitation. At discharge, 24 082 (67.6%) patients were dispensed with < 50% of the target dosage of β-blocker, and 11 530 (32.4%) with ≥ 50% of target dosage.

At the first follow-up 6–10 weeks post MI, patients reported a median EQ5D-I of 0.84 [0.72, 1.00], EQ5D-VAS of 75 [60, 85], and 13 563 (38.1%) reported emotional distress. At second follow-up 12–14 months post MI, patients reported a similar EQ5D-I median of 0.84 [0.72, 1.00], yet a slightly higher EQ5D-VAS of 80 [65, 90] and slightly fewer patients and also a smaller percentage [10 090 (32.9%)] reported emotional distress.

Background characteristics

Descriptive summary statistics in *Table 1* (exposure, in-hospital, and medical history) and *Table 2* (cardiac rehabilitation, SES, and outcomes) show that patients prescribed ≥50% of the target β-blocker dose were more likely to receive metoprolol, have a longer hospital stay, diabetes, hypertension, previous stroke, higher SBP on admission, and be discharged with other medications than those taking <50% of the target β-dose. Patients taking <50% of the target β-blocker dose were more likely to have a higher level of education, be working and have a higher income.

Before imputation and covariate adjustments, observed data in *Figure 2* shows that there were no clear raw associations for any of the three outcomes with the β-blocker dosage exposure across both follow-up time points during cardiac rehabilitation. Left skew and ceiling effects were present for both numeric outcomes (EQ5D-I; EQ5D-VAS) and also bi-/tri-modality (EQ5D-I). There was also a pattern of clustering of individual patient responses at a less granular response level than provided by the EQ5D-VAS, i.e. local response spikes proximal to VAS values 10, 20, 30, et cetera.

Main analysis

After multiple imputation, effect estimates from pooled linear and logistic models were calculated and are presented in *Figure 3*. All estimates apart from female sub-group analysis were statistically significant in the EQ5D-VAS, but there were no differences in the EQ5D-I or Emotional Distress outcomes by level of β-blocker dose when adjusting for pre-defined covariates. This result did not change across both follow-up time points, in men, women, <65 years, and 65–74 year population strata.

Sensitivity analysis

Complete case analysis for the total population is available in the Supplementary material online, *Table A1*.

Results from the analysis of the second patient dispensation are described and reported in the Supplementary material online, *Table A2*, *Figure A1*.

Discussion

The present study investigated the association between HRQoL and β-blocker dose in first time MI patients by studying different aspects of the EQ-5D questionnaire from the SEPHIA registry measured at 6–10 weeks and 12–14 months post MI. We found that neither the EQ-5D Index nor the EQ-5D emotional distress dimension were statistically different between the two β-blocker dose groups. This result remained unchanged at the second follow-up. Only a slight

Table 1 Descriptives for the total patient population and stratified by β-blocker dose with missing values and bivariate significance tests (exposure, in-hospital, and medical history)

	Total	< 50% of the target β-blocker dose	≥ 50% of the target β-blocker dose	P [a]	NA [b]
N	35 612	24 082	11 530		0
β-blocker					
Metoprolol	29 995 (84.2)	21 528 (89.4)	8467 (73.4)	<0.001	0
Bisoprolol	4683 (13.2)	2305 (9.6)	2378 (20.6)	<0.001	0
Atenolol	934 (2.6)	249 (1.0)	685 (5.9)	<0.001	0
Socio-demographics					
Male	26 128 (73.4)	17 612 (73.1)	8516 (73.9)	0.151	0
Age	61.54 (8.65)	61.51 (8.64)	61.60 (8.65)	0.342	0
Smoking status				0.021	832
Never	11 977 (34.4)	8133 (34.5)	3844 (34.3)		
Previous (quit > 1 month)	11 473 (33.0)	7674 (32.5)	3799 (33.9)		
Current	11 330 (32.6)	7772 (33.0)	3558 (31.8)		
Medical history					
BMI	27.60 (4.39)	27.24 (4.24)	28.35 (4.62)	<0.001	3256
Diabetes	4935 (13.9)	2852 (11.9)	2083 (18.1)	<0.001	44
Hypertension	14 182 (40.0)	8310 (34.7)	5872 (51.2)	<0.001	170
Previous stroke	1226 (3.5)	725 (3.0)	501 (4.4)	<0.001	176
Psychiatric history (diagnosis)					
Depression	1507 (4.2)	1036 (4.3)	471 (4.1)	0.357	3
Anxiety	1583 (4.4)	1060 (4.4)	523 (4.5)	0.582	3
Cardiac status					
LVEF				<0.001	5044
≥50%	20 116 (65.8)	14 000 (67.8)	6116 (61.6)		
40–49%	6319 (20.7)	4082 (19.8)	2237 (22.5)		
30–39%	3296 (10.8)	2059 (10.0)	1237 (12.5)		
<30%	837 (2.7)	493 (2.4)	344 (3.5)		
Heart rate	78.2 (19.6)	76.7 (18.7)	81.4 (21.1)	<0.001	1142
SBP	150.55 (28.0)	149.3 (27.4)	153.2 (29.1)	<0.001	1142
Infarct type				0.136	6807
STEMI	12 710 (44.1)	8720 (43.8)	3990 (44.8)		
NSTEMI = (%)	16 095 (55.9)	11 175 (56.2)	4920 (55.2)		
Hospital and cardiac care					
Hospital stay in days [c]	4.00 [3.0, 5.0]	4.0 [3.0, 5.0]	4.0 [3.0, 6.0]	<0.001	0
Reperfusion	15 106 (42.4)	10 165 (42.2)	4941 (42.9)	0.256	1
Revascularization	14 225 (39.9)	9596 (39.8)	4629 (40.1)	0.598	1
Other discharge medications					
ACE inhibitors	24 196 (68.0)	16 251 (67.5)	7945 (69.0)	0.006	25
ARB	4654 (13.1)	2755 (11.4)	1899 (16.5)	<0.001	17
Other antiplatelet medication	33 016 (92.7)	22 473 (93.4)	10 543 (91.4)	<0.001	12
Statins	34 635 (97.3)	23 454 (97.4)	11 181 (97.0)	0.026	3
Comorbid conditions					
Asthma	1355 (3.8)	852 (3.5)	503 (4.4)	<0.001	3
PAD	500 (1.4)	302 (1.3)	198 (1.7)	0.001	3

Data are mean (SD), median [interquartile range], or count (%). Dose is defined by the first β-blocker dispensation.

ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blockers; BMI, body mass index; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

[a]Bivariate comparisons are t-test, Kruskal–Wallis test, and chi-square test for Gaussian numeric, non-Gaussian numeric, and categorical variables, respectively.

[b]Imputed before main analysis.

[c]Time in days from hospital admission to discharge.

Table 2 Descriptives for the total patient population and stratified by β-blocker dose with missing values and bivariate significance tests (cardiac rehabilitation, socioeconomic background, and outcomes)

	Overall	< 50% of the target β-blocker dose	≥ 50% of the target β-blocker dose	P[a]	NA[b]
N	35 612	24 082	11 530		0
Socio-economic status					
Education				<0.001	314
Higher	12 029 (34.1)	8287 (34.7)	3742 (32.7)		
Primary	7181 (20.3)	4732 (19.8)	2449 (21.4)		
Secondary	16 088 (45.6)	10 848 (45.5)	5240 (45.8)		
Income quintile [c]				0.008	227
First	4510 (12.7)	3031 (12.7)	1479 (12.9)		
Second	4159 (11.8)	2775 (11.6)	1384 (12.1)		
Third	6433 (18.2)	4278 (17.9)	2155 (18.8)		
Fourth	9492 (26.8)	6409 (26.8)	3083 (26.9)		
Fifth	10 791 (30.5)	7435 (31.1)	3356 (29.3)		
Occupational status				0.006	206
Working	15 805 (46.6)	10 829 (47.2)	4976 (45.5)		
Sick-leave	988 (2.9)	661 (2.9)	327 (3.0)		
Unemployed	820 (2.4)	555 (2.4)	265 (2.4)		
Retired	16 128 (47.6)	10 791 (47.0)	5337 (48.8)		
Student/other	153 (0.5)	116 (0.5)	37 (0.3)		
Born outside Sweden	5560 (15.6)	3741 (15.5)	1819 (15.8)	0.562	2
First follow-up 6–10 weeks post MI					
EQ5D[e]					
EQ5D-I[f]	0.84 [0.72, 1.00]	0.84 [0.72, 1.00]	0.84 [0.72, 1.00]	<0.001	72
EQ5D-VAS[g]	75.0 [60.0, 85.0]	75.0 [60.0, 85.0]	75.0 [60.0, 82.0]	<0.001	1
Emotional distress[h]	13 563 (38.1)	9060 (37.6)	4503 (39.1)	0.009	0
2nd follow-up 12–14 months after MI					
EQ5D[e]					
EQ-5D Index[f]	0.84 [0.72, 1.00]	0.84 [0.72, 1.00]	0.84 [0.72, 1.00]	<0.001	5014
EQ-5D VAS[g]	80.0 [65.0, 90.0]	80.0 [68.0, 90.0]	75.0 [62.0, 85.0]	<0.001	4950
Emotional distress[h]	10 090 (32.9)	6741 (32.3)	3349 (34.2)	0.001	4943

Data are mean (SD), median [interquartile range], or count (%). Dose is defined by the first post-discharge β-blocker dispensation.
EuroQoL, European Quality of Life association; LDL-C, low-density lipoprotein C; SBP, systolic blood pressure; SEPHIA, Secondary Prevention after Heart Intensive Care Admission.
[a]Bivariate comparisons are *t*-test, Kruskal–Wallis test, and chi-square test for Gaussian numeric, non-Gaussian numeric, and categorical variables, respectively.
[b]Imputed before main analysis.
[c]Income in quintiles for the year preceding the MI and adjusted for family composition (1 = lowest income).
[d]Number of at least moderately intense >30 min sessions of physical activity per week.
[e]EuroQoL Five Dimension scale (1 = 'Indicating no problem [trait 1–5]', 2 = 'Indicating some problems [trait 1–5]', 3 = 'Indicating extreme problems [trait 1–5]').
[f]EuroQoL Index.
[g]EuroQol Visual Analogue Scale.
[h]Emotional Distress, equal to response levels 2 or 3 on the EQ5D Anxiety/Depression item.

statistically significant difference in the EQ-VAS scale scores was found between the two groups, yet clinical meaningfulness of this difference is questionable.

Our findings in this registry-based study suggest there is no difference in outcomes of HRQoL between patients taking <50% or ≥50% of the target β-blocker dose. The EQ-5D-Index takes several aspects into account (such as mobility, pain, and hygiene). However, when taking depression and anxiety into account, as measured by the emotional distress item, our results suggest no major impact of

β-blocker dose on this outcome. This finding, although comparing doses, is predominantly in line with previous findings which have failed to detect an association between β-blockers and HRQoL.[5,7] However, a similar finding to that of the present study was reported by a recent study in patients with atrial fibrillation whereby the EQ-VAS was associated with the β-blocker bisoprolol.[27]

In the present clinical population sample, over 3000 patients were discharged from hospital without β-blocker medication (see *Figure 1*). Since the vast majority (>90%) of MI patients in Sweden
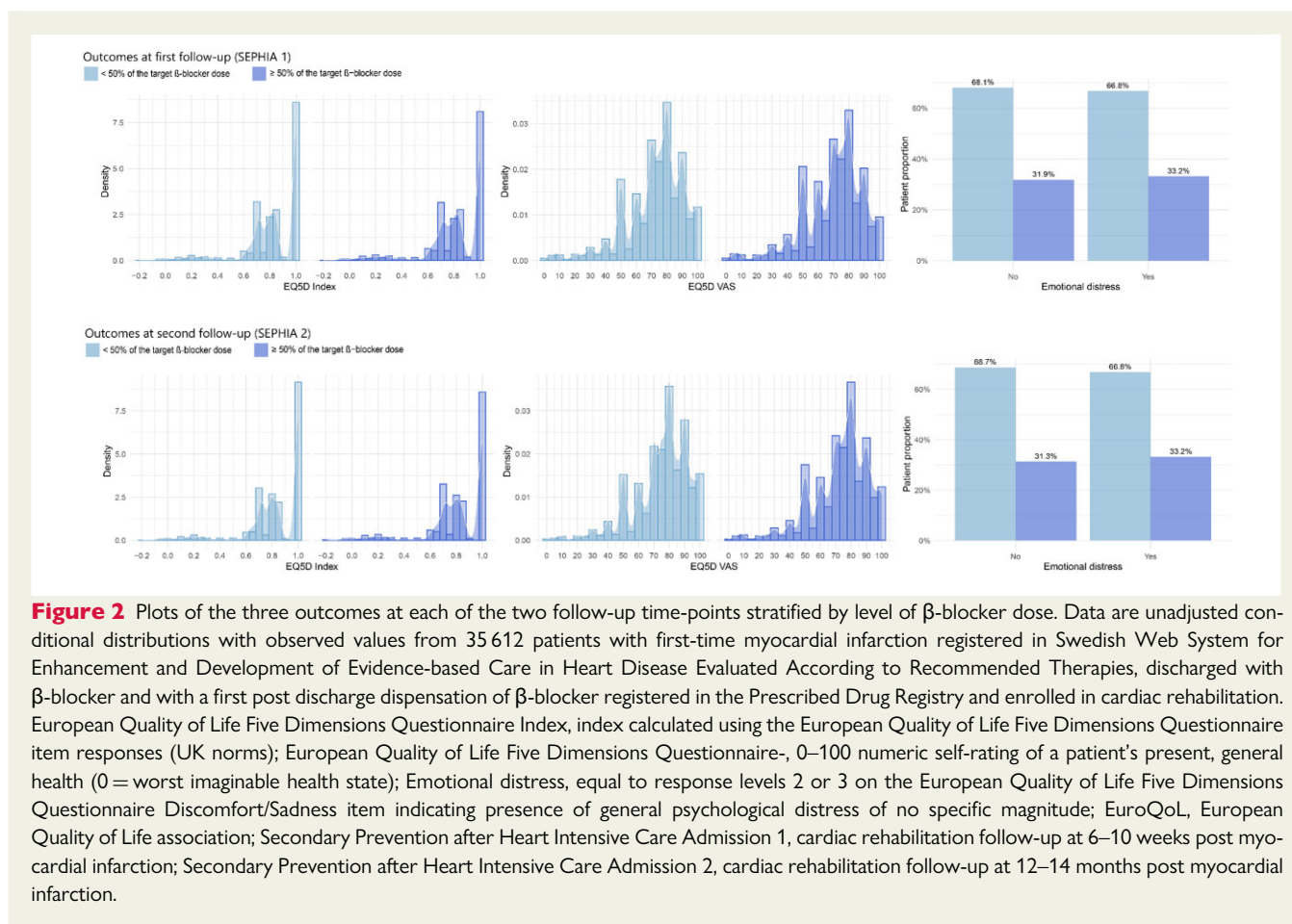
Figure 2 Plots of the three outcomes at each of the two follow-up time-points stratified by level of β-blocker dose. Data are unadjusted conditional distributions with observed values from 35 612 patients with first-time myocardial infarction registered in Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies, discharged with β-blocker and with a first post discharge dispensation of β-blocker registered in the Prescribed Drug Registry and enrolled in cardiac rehabilitation. European Quality of Life Five Dimensions Questionnaire Index, index calculated using the European Quality of Life Five Dimensions Questionnaire item responses (UK norms); European Quality of Life Five Dimensions Questionnaire-, 0–100 numeric self-rating of a patient's present, general health (0 = worst imaginable health state); Emotional distress, equal to response levels 2 or 3 on the European Quality of Life Five Dimensions Questionnaire Discomfort/Sadness item indicating presence of general psychological distress of no specific magnitude; EuroQoL, European Quality of Life association; Secondary Prevention after Heart Intensive Care Admission 1, cardiac rehabilitation follow-up at 6–10 weeks post myocardial infarction; Secondary Prevention after Heart Intensive Care Admission 2, cardiac rehabilitation follow-up at 12–14 months post myocardial infarction.

are discharged with β-blockers by default, it was not possible to compare to patients discharged without β-blockers. For many with clear contraindications such as coronary vasospasm, low blood pressure, bradycardia, or acute heart failure, treatment with β-blockers upon discharge is not recommended,[28] and we would therefore risk confounding the results if we included this third group in the analysis. Similarly, reasons for a low β-blocker dose may be one of several, including: low BMI, sex, asthma, COPD, bradycardia, local treatment traditions, poor patient compliance (etc.). Many of the aforementioned reasons for a lower dose could increase the possibility of confounding if they are also associated with HRQoL; however, we controlled for most of these variables in order to address this potential problem. Contrary to reasons for a lower prescribed dose, our data suggest that those receiving ≥50% of the target dose were more likely to have diabetes, previous stroke, and hypertension, yet controlling for these factors failed to detect any counter-effects of the higher dose on the outcomes measuring HRQoL.

In the present study, the EQ-VAS, a measure of self-reported health and quality of life, although statistically significant, did not indicate any meaningful difference that can be attributed to β-blocker dose that remained after controlling for existing health. The difference in EQ-5D VAS between groups was numerically less than one scale-point (0.87) on a 0–100° scale, intuitively giving little indication of being clinically meaningful. Studies exploring the minimum clinically important difference for the EQ-VAS scale in patients with chronic

medical conditions other than cardiovascular disease generally report larger observed differences than we reported here.[29,30]

HRQoL was measured in the present study by using the EQ-5D instrument. Whilst the ease and simplicity of the EQ-5D is praised in some clinical contexts, the EQ-5D has also been criticized for over-simplification of the outcome and generic classification of health state. Understandably, in comparison with the EQ-5D alone, data-rich standardized questionnaires that delve further into psychological-related health symptoms would be advantageous [such as those used in the QoL sub-study to the ongoing REDUCE-SWEDEHEART trial (NCT03278509)]. However, easy availability of the EQ-5D as a routine measure in the SEPHIA registry allowed for the population size data that was used in the present analysis and thus provides important real-world estimates with high external validity. This thereby complements findings from RCT-designs often suffer from a selection procedure compromising generalizability of findings to the clinical population at large.

Limitations

With registry-based observational data, the risk for unmeasured confounding is always present. We were not able to control for all variables, which may have affected the group allocation and potentially confounded the outcome. This could induce confounding of our estimates if such variables were also associated with HRQoL. On the other hand, we controlled for a wide range of confounders and
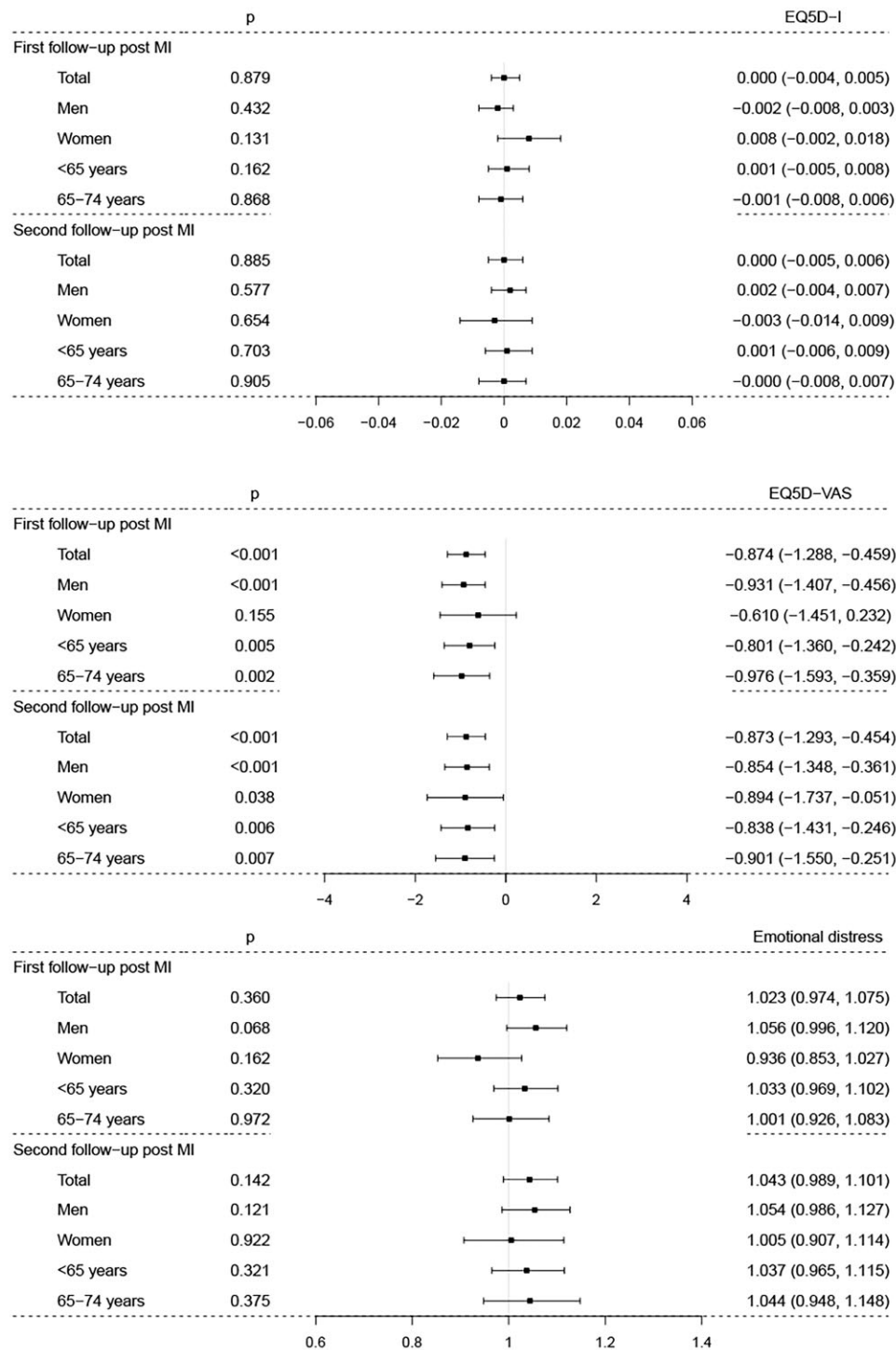
Figure 3 Main adjusted analysis of ≥50% of the target β-blocker dose vs. <50% of the target dose (reference) for outcomes separated by follow-up time. Data are point estimates and 95% confidence intervals with p-values from pooled linear (European Quality of Life Five Dimensions Questionnaire Index, European Quality of Life Five Dimensions Questionnaire-Visual Analogue Scale) or logistic (Emotional distress) regression model estimates after multiple imputation and multivariable adjustment. Three outliers were excluded. Dose is defined by the first post-discharge β-blocker dispensation per each patient. Reference group was patients receiving <50% of the reference β-blocker dose. EQ5D-I, index calculated using the European Quality of Life Five Dimensions Questionnaire item responses (UK norms); European Quality of Life Five Dimensions Questionnaire-Visual Analogue Scale, 0–100 numeric self-rating of a patient's present, general health (0 = worst imaginable health state); Emotional distress, equal to response levels 2 or 3 on the European Quality of Life Five Dimensions Questionnaire Discomfort/Sadness item indicating presence of general psychological distress of no specific magnitude; EuroQoL, European Quality of Life association.

estimates did not change across crude and adjusted analyses. In addition, unlike smaller observational studies with limited data on possible confounders,[31–33] we linked multiple registries in our study which enabled us to control for possible factors that may influence the relationship between β-blocker dose and HRQoL, a method complimented by a similar registry-based study.[9]

Selection bias was possible since we were not able to include patients above 75 years in the analysis at the dates we used for inclusion. Although the SEPHIA register now includes patients <80 years, our analysis covered dates outside of this period. Many women experience MI at a later stage in life than men, it might thus be a disadvantage that the age group 75–80 years is not included in our analysis, especially since the stratification analysis for female sex was the only sub-group that showed no association between β-blocker dose and EQ-VAS outcomes at first follow-up.

On the contrary, our findings in patients <75 years might have important implications in men. β-blocker consumption has been negatively associated with erectile dysfunction (ED) in younger men, when compared with those not taking the medication,[34] and to those in an older age category.[35] This seems to be a common finding[36] that is specific to β-blockers than to other antihypertensive medication, such as ACE inhibitors.[37] This relationship is important to consider seeing that HRQoL is reportedly lower in people with ED[38,39] and could therefore be important for the present study's findings in patients aged <75 years.

Lastly, comparing high to low dose classifications can only tell us so much about the effect of β-blocker on HRQoL, and there is no way to monitor the exact dose consumed to the dose implied by the prescription dispensation, although we can assume accuracy is rather good. β-blocker adherence has been found to significantly decline over time after discharge.[40,41] Reasons for this decline could be due to unwanted side effects, but since the present study did not find the results to differ to any large extent when conducting sensitivity analyses on the second outtake of β-blocker, actual vs. presumed consumption is unlikely to have impacted our findings to a substantial degree. Randomized trials [such as the ongoing trials: Swedish Randomized Evaluation of Decreased Usage of β-blockers after MI in the SWEDEHEART registry (REDUCE-SWEDEHEART, NCT03278509) and the Treatment with Beta-blockers after Myocardial Infarction without Reduced Ejection Fraction (REBOOT, NCT03596385[42])] remain the best method of directly comparing actual effects of treatment vs. no treatment at all (or even placebo) in this context. Whilst it is difficult to infer causation from non-randomized studies, this observational study has the benefit of using nationwide, real-world data from over 35 000 first-time MI patients and can therefore compliment smaller, more narrowly selected RCTs in this area.

Conclusion

This large national real-world cohort study on first-time MI patients did not detect a difference in the EQ-5D index between those receiving low vs. high β-blocker dose either at short- or long-term following discharge. Only a small significant difference was found in the EQ-5D VAS. Thus, it seems likely that there is no clinically meaningful relationship between level of β-blocker post-MI discharge and self-assessed HRQoL.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

Data availability

Due to legal reasons, the data in the article cannot be shared publicly.

Authors' contributions

All authors were responsible for the concept and design, critical revising of the manuscript, and result interpretation. J.W., C.H. and E.M.G.O. were responsible for data acquisition. S.H. and J.W. drafted the manuscript. J.W. did the statistical analyses. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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