Supplementary Appendix

Supplement to: Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa2401479

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix to:

Beta-blockers after Myocardial Infarction and Preserved Ejection Fraction

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SUPPLEMENTARY APPENDIX

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The data safety monitoring board (DSMB) independently ensured the safety of the intervention as well as the general execution of the trial on behalf of the trial participants. The responsibilities of the DSMB were defined in a separate charter agreed upon by the steering committee and the DSMB members. Outcome analyses for the DSMB have been performed after 2 and 4 years of recruitment.

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Description of the SWEDEHEART registries and data fidelity

SWEDEHEART

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) was established in December 2009 through a merger of four Swedish health registries; the national registry of acute cardiac care (RIKS-HIA), the Swedish coronary angiography and angioplasty registry (SCAAR), the Swedish heart surgery registry, and the national registry of secondary prevention (SEPHIA). The first registries to collect data for cardiovascular care in Sweden was RIKS-HIA, established in 1990, and the Swedish heart surgery registry, formed in 1992. RIKS-HIA became a National quality registry in 1995 after which SEPHIA was added to the registry in 2005 to provide information on secondary prevention efforts in patients with acute myocardial infarction. SCAAR was established in 1998 by joining of a national angioplasty registry and a national coronary angiography registry, formed in the early 1990s. Three additional registries have been added to the SWEDEHEART family since 2009; SWENTRY (the SWEdish traNscatheter cardiac intervention registry) established in 2008, SwedeHF (the Swedish Heart Failure Registry) formed in 2001, and the Swedish National Cardiogenetic Registry. The cardiogenetic registry is still under development but has started to register adult patients with familiar hypercholesterolemia during the last years.

Organization and funding

Each registry that is part of SWEDEHEART is run by a working group with a leading chairman. The chairman represents their registry in the SWEDEHEART steering group, which also consists of representatives from the Swedish Heart Association, the Swedish

Society of Cardiac Nurses, and the Swedish Heart and Lung Association, an organization for patients with cardiovascular disease. Project management, quality controls, and statistical reports are handled by Uppsala Clinical Research Center (UCR), provider of the technical solution (web forms and database). Monitoring is performed by experienced cardiac nurses and coordinated by UCR. The registry is supported by the Swedish Society of Cardiology, the Swedish Society of Thoracic Radiology, the Swedish Society of Thoracic Surgery, and the Swedish Heart Association. The registry is financed by the Swedish Association of Local Authorities and Regions (SALAR), the Swedish State and the Swedish Heart-Lung Foundation. Each participating hospital handles the cost of local data entry without financial support from the registry.

Data

All Swedish hospitals that practice acute coronary care and cardiac surgery (74 hospitals in 2022) participate in SWEDEHEART by registering patients admitted to the hospital for symptoms of an acute coronary syndrome (ACS) and patients undergoing coronary angiography/angioplasty or heart surgery. The registry enrolls approximately 100,000 cases each year: 20,000 with ACS, 8,000 with heart failure, 65,000 undergoing coronary angiography or angioplasty, 6,000 undergoing heart surgery, and 8,000 who are followed for 11-13 months regarding secondary prevention after an ACS. All patient data are kept in one record, even if the patient is transferred between different units and hospitals during the care process. Patient data are entered online by the caregiver and transferred in an encrypted format to a central server. SWEDEHEART has also begun direct data transfer from electronic health records to the registry in parts of Sweden.

For patients admitted to hospital because of symptoms suggestive of an ACS information is collected prospectively for 112 variables in RIKS-HIA and include patient demographics, admission logistics, risk factors, past medical history, medical treatment prior to admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses and discharge-medications. For patients younger than 80 years who have been hospitalized for ACS a follow-up visit is performed after 6-10 weeks and again after 11-13 months. From these visits approximately 80 new variables are added in SEPHIA. For patients undergoing coronary angiography/angioplasty for any clinical indication, approximately 150 variables are registered in SCAAR.

Patient identification

The unique personal identification number of Swedish citizens is included in SWEDEHEART when registering a new patient. Together with information on the patient's name and address, and the identity of the admitting hospital, the SWEDEHEART database can be merged with the Swedish population registry to provide data about vital status and emigration, the National Cause of Death Register for data about cause of death and the National Patient Registry, to collect information on diagnoses (ICD codes) on all admissions in Sweden since 1987. Because the merger and complete follow-up required a personal identification number, only Swedish residents were eligible for the REDUCE trial in Sweden. The merger of the different registries is approved by the National Board of Health and Welfare and the Swedish Ethical Review Authority. Furthermore, the patient receives information about their participation in the registry and has the right to decline participation. Patient identity is never released to the researchers, who only gain access to information on hospital identity.

Data quality

SWEDEHEART and UCR provides manuals, education, and technical advice to users of the SWEDEHEART registry. The information is available on the SWEDEHEART website (https://www.ucr.uu.se/swedeheart/) and through a telephone help desk. To aid health care providers with data entry, definitions for each variable are easily accessible and the system routinely checks for range and consistency errors. The correctness of data for all hospitals is monitored every three years. The overall correctness between data registered in SWEDEHEART and the electronic health records of individual patients is >90%, the exact numbers for the latest monitoring period are found below.

SWEDEHEART data correctness during 2017-2018, with number of patients, variables, and hospitals monitored for each registry.

SWEDEHEART registry	No. of patients	No. of variables	No. of hospitals	Overall data correctness
RIKS-HIA	30	63	72	97.1%
SCAAR	30	104	30	98.2%
SEPHIA	20	29	74	94.8%

A new monitoring period started in 2019 but had to be interrupted in 2020 due to the COVID-19 pandemic. Thus, there is a lack of monitoring data for the years 2019 and 2020, but monitors resumed their work in 2021 when hospitals allowed in person visits.

Most patients with ACS are captured in SWEDEHEART (>90%), but because some patients are admitted to hospital departments other than cardiac care units there is still some variation between hospitals in completeness of data. Patients with type-1 myocardial infarction and younger than 80 years of age are also registered and followed to a higher degree than older patients and those with type-2 myocardial infarction.

Use of SWEDEHEART data

The purpose of the SWEDEHEART registry is principally to support evidence-based improvements in health care. This is done by providing continuous information on national care needs and therapy results and any observed changes within and between hospitals. The long-term goal of the registry has always been to contribute to decreased mortality and morbidity among patients and to increase cost effectiveness in coronary care. Hospitals participating in SWEDEHEART are each year evaluated through a Quality Index, which gives points according to, among others, the percentage of patients that have been entered in the registry and properly followed through the care process. The Quality Index results are published online in a yearly report (https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh), which allows hospitals to compare their processes of care and outcomes with other hospitals, and implement changes where needed. The published results have also been noted by media and authorities, which has led to further improvements in health care both locally and nationally.

SWEDEHEART data is primarily used to review the positive effects and limitations of the present-day health care system, but with new Registry-based RCT studies can also be used to develop new techniques and treatment methods for cardiovascular care. Investigators are allowed to use SWEDEHEART data for research purposes after approval from the steering committee and the Swedish Ethical Review Authority. To apply for data export from SWEDEHEART, the researcher should fill out a form "Application for registry data for research" (https://www.ucr.uu.se/sv/tjanster/blanketter-och-dokument) and submit it to datauttag@ucr.uu.se.

Data handling in ESTONIA and NEW ZEALAND

In Estonia and New Zealand, baseline data were manually entered into an eCRF, with the same structure as the SWEDEHEART registry, and follow-up was performed from health records from the hospital providing care for the patient.

Electronic Data Capture System (EDC)

ClinCapture version 2.2.5 was used for creating the study design and data entry database and for data processing. ClinCapture is developed by ClinCapture.

ClinCapture consists of different modules: Test and Production. Test is used for creating the data entry environment and for the training of users. Production is used for data entry of study data. EDC ClinCapture is compliant with core 21 CFR Part 11 requirements and meets all FDA requirements. ClinCapture version 2.1 is validated by UCR.

Location of EDC system

The EDC system is cloud-based and supplier ClinCapture is responsible for all system maintenance and supervision.

REDUCE study instance of EDC is accessed by logging into:

https://eu.clincapture.com/reduce

The study database for REDUCE is located on Amazon servers. ClinCapture is hosted on Amazon RDS in the EU.

Outcome definitions

Guidance for definition of acute myocardial infarction

The definition is based on Fourth Universal myocardial infarction (MI) definition.[1] The term acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any 1 of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI-related MI is arbitrarily defined by elevation of cTn values (> 5 x 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. In addition, either
    - symptoms suggestive of myocardial ischemia, or
    - new ischemic ECG changes, or
    - angiographic findings consistent with a procedural complication, or

    - imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL
- CABG- related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 x 99th percentile URL) in patients with normal baseline cTn values (≤ 99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Termination of the Study

Based on monitoring of observed events, the steering committee decided to stop inclusion on 4 May 2023 with 5020 participants. End-of-study follow up was performed between March 8 and 16, 2023, in Estonia, and between October 20 and November 16 in New Zealand. On November 13, 2023 the steering committee noted that the target number of events had been reached, and set the date of the previous last SWEDEHEART extraction, November 4, as data cut-off for Sweden.

Supplemental Details on Statistical Analysis

We allocated no alpha to the interim safety analyses, since stopping was only allowed for unforeseen safety concerns related to trial participation, and explicitly not because of emerging differences between the treatments. Comparisons of outcomes between the treatment arms were restricted to the DSMB and an independent reporting statistician not otherwise involved with the trial.

Censoring clinical event outcomes for withdrawal or emigration assumes that this censoring is independent of treatment arm, alternatively independent of future risk conditional on treatment arm. We predefined no sensitivity analyses for loss to follow-up since we knew from the event monitoring that loss to follow-up was minimal, see Figure S1. Post-hoc we performed sensitivity analyses of the primary outcome, counting loss to follow-up as an event, in either or both arms. As expected, the conclusions were robust, see Table S7.
For NYHA and CCS score measured in Sweden, loss to follow-up was more substantial, see Figure S1. NYHA and CCS score were analyzed using proportional odds logistic regression, with supplemental binary logistic regressions for all cut-points. The primary analysis uses observed cases, which assumes scores are missing at random conditional on treatment arm, alternatively that the missing scores are independent of treatment arm. We performed

sensitivity analyses of NYHA and CCS scores for a number of scenarios where missing data was imputed differently between the arms, using missing-not-at-random (MNAR) multiple imputation. For practical reasons, the analyses were performed for the individual binary logistic regressions. The multiple imputation used the logistic regression method with treatment arm as the only predictor. For each analysis, 25 data sets were imputed and analyzed using unadjusted logistic regression, and the results were combined using Rubin's rules. The MNAR scenarios consisted of imputing missing observations in the Beta-blocker arm with the odds of worse score multiplied by between 0.1 and 10, while not changing the odds for the No Beta-blocker arm, and the results are shown in Table S8-S11. For CCS, the conclusions were robust (nominal confidence intervals including one) up to about 50% higher odds of worse score in the unobserved patients in the beta-blocker arm, compared to the no beta-blocker arm. For NYHA score, the conclusions were robust up to about twice that bias. To account for the competing risk of non-CV death in the analysis of CV death, and the competing risk of death before outcome for all outcomes except the primary composite and all-cause death, we estimate cause-specific hazard ratios for these outcomes. Cumulative incidence of non-CV death, which is the cause competing with CV death, is presented in Figure S12. The competing causes for the other outcomes, death before the particular outcome, are presented in Figure S13.

Trial organization and process of writing the manuscript

The steering group designed the trial, and the trial protocol and the statistical analysis plan are available at nejm.org. Trial support, including project coordination, data management, statistical oversight and analyses were performed by the Uppsala Clinical Research center (UCR). Monitoring was performed by UCR and the Clinical Research Center at Danderyd Hospital, Stockholm, in Sweden, by Lepritech OÜ, Tabasalu, in Estonia, and by the

Cardiovascular Research Unit, Auckland City Hospital in New Zealand. Ethical review boards approved the trial in each country.

The first and the last author provided the first draft of the manuscript and all authors critically revised and finally approved the submitted manuscript. All authors take responsibility for the accuracy and completeness of data. The funders were not involved in interpreting the results or the writing of the manuscript.

Table S1. **REDUCE-AMI inclusion/exclusion criteria**

Inclusion criteria
1. Men or women age ≥18 at the time of signing the informed consent 2. Day 1-7 after MI, either ST elevation MI or non-ST-elevation MI, according to the fourth universal definition of MI,[1] type 1. 3. Coronary angiography performed during hospitalization. 4. Obstructive coronary artery disease documented by coronary angiography, i.e. stenosis ≥ 50 %, FFR ≤ 0.80 or iFR ≤ 0.89 in any segment at any time point before randomization. 5. Echocardiography performed after the MI showing a normal ejection fraction defined as EF≥50%. 6. Written informed consent obtained
Exclusion criteria
1. Any condition that may influence the patient's ability to comply with study protocol. 2. Contraindications for beta-blockade 3. Indication for beta-blockade other than as secondary prevention according to the treating physician

Table S2. **Outcomes**

	In primary report
Primary Composite Outcome	
1. All-cause death or new MI	Yes
Secondary Outcomes	
1. All-cause death	Yes
2. Cardiovascular Death (ICD 10 codes: I00-I99)	Yes
3. New MI	Yes
4. Heart failure hospitalization (ICD 10 code: I50, primary diagnosis)	Yes
5. Atrial fibrillation hospitalization (ICD 10 code: I48, primary diagnosis)	Yes
For those followed in the secondary prevention part of SWEDEHEART (in Sweden):	
1. Dyspnea (NYHA-class)	Yes
2. Angina (CCS-class)	Yes
3. Health related quality of life (EQ-5D)	No
4. Health care costs	No
Safety Outcome	
Hospitalization due to	
1. Bradycardia (ICD 10 codes: R00.1, I49.5), AV-block II-III (ICD 10 codes: I44.1-3), Hypotension (ICD 10 code: I95), Syncope (ICD 10 codes: R55.9, T67.1) or Need for pacemaker (ICD 10 codes: FPE00-26, FPF00-20, TFP00)	Yes
2. Asthma (ICD 10 codes J45-46, primary diagnosis) or COPD (ICD 10 code: J44, primary diagnosis)	Yes
3. Stroke (ICD 10 codes: I60-64)	Yes

Table S3. **Missing or unknown baseline data**

Characteristic	Beta- blockers (n=2508)		No Beta-blockers (n=2512)	
Demography				
Age	0	(0)	0	(0)
Female sex, no (%)	0	(0)	0	(0)
Country				
Sweden	0	(0)	0	(0)
Estonia	0	(0)	0	(0)
New Zealand	0	(0)	0	(0)
Risk Factors				
Current smoker, no (%)	42	(1.7)	29	(1.2)
Hypertension, no (%)	1	(0.0)	3	(0.1)
Diabetes mellitus, no (%)	2	(0.1)	3	(0.1)
Prior cardiovascular disease				
Prior myocardial infarctions, no (%)	5	(0.2)	5	(0.2)
Prior PCI,	4	(0.2)	7	(0.3)
Prior CABG,	4	(0.2)	5	(0.2)
Prior Stroke, no (%)	2	(0.1)	5	(0.2)
Prior Heart failure, no (%)	22	(0.9)	31	(1.2)
Presentation characteristics				
Chest pain as main symptoms, no (%)	1	(0.0)	0	(0)
CPR before hospital, no (%)	25	(1.0)	27	(0.1)
Pulmonary rales, no (%)	63	(2.5)	50	(2.0)
Heart rate, median (IQR)	19	(0.8)	17	(0.7)
Systolic blood pressure, median (IQR)	23	(0.9)	22	(0.9)
Atrial fibrillation, no (%)	6	(0.2)	8	(0.3)
ST-elevation MI, no (%)	1	(0.0)	0	(0)
On oral beta-blocker treatment, no (%)	40	(1.6)	40	(1.6)
Days from hospital admission to randomization, median (IQR)	0	(0)	0	(0)
In-hospital Course				
Coronary angiography				
No stenosis	24	(1.0)	21	(0.8)
1-vessel disease, no (%)	24	(1.0)	21	(0.8)
2-vessel disease, no (%)	24	(1.0)	21	(0.8)
LM or 3-vessel disease, no (%)	24	(1.0)	21	(0.8)
Percutaneous coronary intervention	17	(0.7)	16	(0.6)
Coronary artery by-pass grafting, no (%)	17	(0.7)	16	(0.6)
Medication at discharge				
Aspirin, no (%)	1	(0.0)	0	(0)
P2Y12-rec blockade, no (%)	1	(0.0)	0	(0)
Beta-blockade, no (%)	3	(0.1)	0	(0)
ACEI or ARB, no (%)	1	(0.0)	0	(0)
ARB, no (%)	1	(0.0)	0	(0)
Statins, no (%)	1	(0.0)	2	(0.1)
Diuretics, no (%)	1	(0.0)	0	(0)
Calcium channel blocker	0	(0)	1	(0.0)

IQR: interquartile range, PCI: percutaneous coronary intervention, CABG: coronary artery by-pass grafting, CPR: cardiopulmonary resuscitation, LM: left main, ACEI: Angiotensin-converting-enzyme inhibitors, ARB: Angiotensin receptor blockers. Race and ethnicity were not collected.

Table S4, **Missing data or unknown during follow-up in those who attended the SWEDEHEART registry follow-up visits in Sweden.**

Characteristic	Beta- blocker (n=2508)		No Beta-blockers (n=2512)	
Beta-blocker treatment				
6-10 weeks	3/1909	(0.2)	3/1927	(0.2)
12-14 months	3/1834	(0.2)	0/1886	(0)

See Figure S1 (Consort diagram) regarding the number of individuals who were invited to the SWEDEHEART registry follow-up visits

Table S5. Adjusted analyses for the primary outcome, ITT

Model	**Hazard ratio**	**95%CI**
Adjusted for country	0.96	(0.79-1.16)
Adjusted for age as a restricted cubic spline, diabetes mellitus and previous MI	0.96	(0.80-1.17)

Table S6: Representativeness of the study population

Category	
Condition under investigation	Myocardial infarction, type 1, with preserved ejection fraction, undergoing coronary angiography
Special considerations related to	
Sex and gender	In contemporary studies, including unselected patients, 25-40% of patients with ST-elevation MI and 30-45% of patients with non-ST-elevation MI are women (1-3). In patients with preserved ejection fraction the proportion of women is lower (4).
Age	In contemporary studies, including unselected patients, median age has been 64-70 years in patients with ST-elevation MI and 68-75 years in patients with non-ST-elevation MI (ref). In patients with preserved EF, the median age is lower (4).
Geography	Baseline characteristics and treatments vary between countries, including the proportion undergoing angiography and subsequent revascularization (1-3).
Other considerations	Excluding individuals with contraindications (e.g. bradyarrhythmia) or indications other than secondary prevention after myocardial infarction (e.g. tachyarrhythmia) of bet-blocker treatment, will further lower the risk of the study population.
Overall representativeness of this trial	The distribution of age, sex other baseline characteristics are similar to what have been found in observational studies including unselected patients with myocardial infarction and preserved ejection fraction (4). However, the event rate was lower than expected

Information about race and ethnicity were not collected.

1. Eur Heart J Qual Care Clin Outcomes. 2022 Jun 6;8(4):429-436, 2. Eur Heart J Qual Care Clin Outcomes. 2022 May 5;8(3):307-314, 3.Circulation 2017; 136: 1908-1919, 4. Eur Heart J Qual Care Clin Outcomes. 2019;5:12-20.

Table S7. Sensitivity analyses for loss to follow-up of the primary outcome, ITT

Model	Hazard ratio	95%CI
Censored for loss-to-follow-up (predefined analysis)	0.96	(0.79-1.16)
Loss-to-follow-up as event in both arms	0.95	(0.79-1.15)
Loss-to-follow-up as event in the Beta-blocker arm	0.98	(0.81-1.19)
Loss-to-follow-up as event in the No Beta-blocker arm	0.92	(0.76-1.12)

Table S8. Sensitivity analyses of NYHA score at 6-10 weeks.

	NYHA I-IV vs No	NYHA II-IV vs No-NYHA I	NYHA III-IV vs No-NYHA II	NYHA IV vs No-NYHA III
Observed Cases	**1.19 (0.95; 1.48)**	**1.17 (0.90; 1.54)**	**1.06 (0.56; 2.01)**	**2.53 (0.54; 17.66)**
Odds increase	**Result from MNAR multiple imputation**			
0.1	1.04 (0.84; 1.29)	1.03 (0.79; 1.34)	0.95 (0.50; 1.79)	2.26 (0.44; 11.49)
0.12	1.04 (0.84; 1.29)	1.03 (0.79; 1.35)	0.95 (0.50; 1.79)	2.28 (0.45; 11.59)
0.2	1.05 (0.85; 1.31)	1.04 (0.80; 1.36)	0.96 (0.51; 1.81)	2.31 (0.45; 11.81)
0.25	1.06 (0.86; 1.31)	1.05 (0.80; 1.37)	0.97 (0.51; 1.82)	2.33 (0.46; 11.83)
0.33	1.07 (0.87; 1.33)	1.06 (0.81; 1.39)	0.98 (0.52; 1.86)	2.38 (0.47; 12.05)
0.5	1.10 (0.89; 1.36)	1.09 (0.83; 1.42)	1.01 (0.53; 1.90)	2.41 (0.48; 12.19)
0.67	1.13 (0.92; 1.40)	1.11 (0.85; 1.45)	1.03 (0.54; 1.97)	2.44 (0.48; 12.42)
0.8	1.15 (0.93; 1.43)	1.13 (0.87; 1.47)	1.05 (0.55; 1.98)	2.46 (0.48; 12.52)
0.91	1.17 (0.94; 1.45)	1.15 (0.88; 1.49)	1.06 (0.56; 2.01)	2.54 (0.50; 12.96)
0.95	1.18 (0.95; 1.45)	1.15 (0.89; 1.50)	1.06 (0.56; 2.02)	2.57 (0.51; 13.09)
1	1.18 (0.96; 1.46)	1.16 (0.89; 1.51)	1.07 (0.56; 2.02)	2.59 (0.51; 13.08)
1.05	1.19 (0.97; 1.47)	1.17 (0.90; 1.52)	1.07 (0.56; 2.04)	2.62 (0.52; 13.30)
1.1	1.20 (0.97; 1.49)	1.18 (0.91; 1.53)	1.08 (0.56; 2.05)	2.64 (0.52; 13.41)
1.25	1.23 (0.99; 1.51)	1.20 (0.93; 1.56)	1.09 (0.57; 2.08)	2.69 (0.53; 13.67)
1.5	1.26 (1.02; 1.55)	1.24 (0.95; 1.61)	1.12 (0.60; 2.10)	2.70 (0.53; 13.80)
2	1.32 (1.07; 1.62)	1.32 (1.02; 1.70)	1.18 (0.63; 2.19)	2.92 (0.57; 14.89)
3	1.44 (1.17; 1.77)	1.43 (1.11; 1.85)	1.31 (0.71; 2.42)	3.21 (0.63; 16.41)
4	1.54 (1.25; 1.89)	1.54 (1.20; 1.98)	1.43 (0.78; 2.62)	3.42 (0.67; 17.42)
5	1.62 (1.32; 1.99)	1.65 (1.29; 2.12)	1.55 (0.84; 2.85)	3.65 (0.73; 18.24)
8	1.82 (1.48; 2.23)	1.90 (1.49; 2.43)	1.92 (1.03; 3.56)	4.49 (0.91; 22.13)
10	1.92 (1.57; 2.35)	2.04 (1.60; 2.60)	2.18 (1.19; 3.98)	5.23 (1.07; 25.56)

MNAR multiple imputation: In the No Beta-blocker arm, missing observations were imputed from the observed odds of bad outcome in that arm, while in the Beta-blocker arm, missing observations were imputed from the observed odds times the Odds increase factor.

Table S9. Sensitivity analyses of NYHA score at 11-13 months.

	NYHA I-IV vs No	NYHA II-IV vs No-NYHA I	NYHA III-IV vs No-NYHA II	NYHA IV vs No-NYHA III
Observed Cases	**1.23 (0.97; 1.55)**	**0.96 (0.70; 1.30)**	**0.76 (0.37; 1.51)**	**0.41 (0.06; 1.91)**
Odds increase	**Result from MNAR multiple imputation**			
0.1	1.02 (0.81; 1.30)	0.80 (0.59; 1.10)	0.64 (0.32; 1.27)	0.34 (0.07; 1.79)
0.12	1.03 (0.81; 1.31)	0.81 (0.59; 1.11)	0.64 (0.32; 1.28)	0.34 (0.07; 1.79)
0.2	1.05 (0.82; 1.33)	0.82 (0.60; 1.13)	0.65 (0.32; 1.31)	0.35 (0.07; 1.83)
0.25	1.06 (0.83; 1.34)	0.83 (0.60; 1.14)	0.66 (0.33; 1.33)	0.36 (0.07; 1.89)
0.33	1.07 (0.84; 1.36)	0.84 (0.61; 1.16)	0.68 (0.34; 1.36)	0.36 (0.07; 1.92)
0.5	1.10 (0.87; 1.40)	0.87 (0.63; 1.20)	0.69 (0.34; 1.38)	0.37 (0.07; 1.95)
0.67	1.13 (0.89; 1.44)	0.89 (0.65; 1.23)	0.71 (0.35; 1.43)	0.38 (0.07; 1.99)
0.8	1.17 (0.92; 1.49)	0.91 (0.66; 1.26)	0.73 (0.36; 1.45)	0.40 (0.07; 2.17)
0.91	1.19 (0.93; 1.51)	0.93 (0.67; 1.28)	0.74 (0.37; 1.50)	0.40 (0.07; 2.21)
0.95	1.20 (0.94; 1.53)	0.93 (0.68; 1.29)	0.75 (0.37; 1.51)	0.42 (0.08; 2.30)
1	1.21 (0.95; 1.54)	0.94 (0.68; 1.30)	0.76 (0.37; 1.54)	0.42 (0.08; 2.30)
1.05	1.22 (0.96; 1.55)	0.95 (0.69; 1.31)	0.76 (0.37; 1.55)	0.42 (0.08; 2.30)
1.1	1.23 (0.97; 1.56)	0.95 (0.69; 1.32)	0.76 (0.37; 1.56)	0.42 (0.08; 2.34)
1.25	1.26 (0.99; 1.60)	0.97 (0.71; 1.34)	0.80 (0.38; 1.65)	0.43 (0.08; 2.43)
1.5	1.31 (1.03; 1.66)	1.00 (0.73; 1.39)	0.83 (0.40; 1.72)	0.47 (0.08; 2.66)
2	1.39 (1.08; 1.78)	1.09 (0.78; 1.51)	0.89 (0.42; 1.87)	0.50 (0.09; 2.83)
3	1.54 (1.21; 1.97)	1.23 (0.89; 1.70)	1.01 (0.48; 2.10)	0.55 (0.09; 3.34)
4	1.68 (1.33; 2.14)	1.35 (0.97; 1.88)	1.10 (0.53; 2.31)	0.63 (0.10; 4.10)
5	1.81 (1.43; 2.29)	1.47 (1.06; 2.03)	1.21 (0.58; 2.53)	0.71 (0.10; 4.99)
8	2.09 (1.65; 2.64)	1.78 (1.30; 2.44)	1.53 (0.72; 3.22)	0.92 (0.13; 6.64)
10	2.24 (1.76; 2.83)	1.97 (1.45; 2.69)	1.73 (0.80; 3.72)	1.03 (0.14; 7.37)

MNAR multiple imputation: In the No Beta-blocker arm, missing observations were imputed from the observed odds of bad outcome in that arm, while in the Beta-blocker arm, missing observations were imputed from the observed odds times the Odds increase factor.

Table S10. Sensitivity analyses of CCS score at 6-10 weeks.

	CCS I-IV vs No	CCS II-IV vs No-CCS I	CCS III-IV vs No-CCS II
Observed Cases	**1.00 (0.77; 1.30)**	**1.24 (0.77; 1.99)**	**2.02 (0.72; 6.51)**
Odds increase	**Result from MNAR multiple imputation**		
0.1	0.90 (0.70; 1.16)	1.13 (0.71; 1.80)	1.84 (0.63; 5.39)
0.12	0.90 (0.70; 1.17)	1.13 (0.71; 1.81)	1.86 (0.63; 5.45)
0.2	0.91 (0.71; 1.18)	1.15 (0.72; 1.84)	1.89 (0.65; 5.51)
0.25	0.92 (0.71; 1.19)	1.15 (0.72; 1.85)	1.89 (0.65; 5.51)
0.33	0.93 (0.72; 1.20)	1.17 (0.73; 1.88)	1.90 (0.65; 5.52)
0.5	0.95 (0.74; 1.23)	1.20 (0.75; 1.93)	1.96 (0.68; 5.68)
0.67	0.97 (0.75; 1.26)	1.22 (0.76; 1.97)	2.01 (0.69; 5.82)
0.8	0.99 (0.76; 1.28)	1.24 (0.77; 2.00)	2.06 (0.71; 5.97)
0.91	1.00 (0.77; 1.30)	1.25 (0.78; 2.02)	2.10 (0.73; 6.09)
0.95	1.01 (0.78; 1.31)	1.26 (0.78; 2.03)	2.12 (0.73; 6.14)
1	1.02 (0.78; 1.32)	1.28 (0.79; 2.05)	2.14 (0.73; 6.22)
1.05	1.02 (0.79; 1.33)	1.28 (0.80; 2.06)	2.15 (0.74; 6.26)
1.1	1.03 (0.80; 1.34)	1.30 (0.81; 2.08)	2.17 (0.74; 6.34)
1.25	1.05 (0.81; 1.36)	1.32 (0.82; 2.11)	2.18 (0.75; 6.35)
1.5	1.08 (0.83; 1.40)	1.36 (0.85; 2.17)	2.24 (0.76; 6.55)
2	1.14 (0.88; 1.47)	1.42 (0.89; 2.28)	2.39 (0.80; 7.08)
3	1.25 (0.97; 1.62)	1.57 (0.97; 2.52)	2.59 (0.87; 7.68)
4	1.36 (1.04; 1.76)	1.72 (1.07; 2.76)	2.86 (0.95; 8.66)
5	1.44 (1.11; 1.88)	1.87 (1.17; 2.99)	3.09 (1.02; 9.35)
8	1.66 (1.29; 2.13)	2.28 (1.42; 3.65)	3.84 (1.31; 11.30)
10	1.77 (1.37; 2.29)	2.53 (1.59; 4.02)	4.22 (1.40; 12.66)

MNAR multiple imputation: In the No Beta-blocker arm, missing observations were imputed from the observed odds of bad outcome in that arm, while in the Beta-blocker arm, missing observations were imputed from the observed odds times the Odds increase factor.

Table S11. Sensitivity analyses of CCS score at 11-13 months.

	CCS I-IV vs No	CCS II-IV vs No-CCS I	CCS III-IV vs No-CCS II	CCS IV vs No-CCS III
Observed Cases	**1.07 (0.82; 1.39)**	**1.06 (0.68; 1.65)**	**1.03 (0.46; 2.32)**	**1.29 (0.34; 5.21)**
Odds increase	**Result from MNAR multiple imputation**			
0.1	0.90 (0.70; 1.17)	0.88 (0.57; 1.37)	0.86 (0.38; 1.92)	1.08 (0.28; 4.07)
0.12	0.91 (0.70; 1.17)	0.89 (0.57; 1.38)	0.86 (0.38; 1.92)	1.08 (0.29; 4.09)
0.2	0.92 (0.71; 1.19)	0.90 (0.58; 1.40)	0.86 (0.38; 1.92)	1.10 (0.29; 4.18)
0.25	0.93 (0.71; 1.20)	0.91 (0.58; 1.41)	0.87 (0.39; 1.95)	1.11 (0.29; 4.20)
0.33	0.94 (0.72; 1.22)	0.92 (0.59; 1.44)	0.87 (0.39; 1.96)	1.11 (0.29; 4.20)
0.5	0.97 (0.75; 1.26)	0.94 (0.60; 1.46)	0.90 (0.40; 2.03)	1.11 (0.29; 4.20)
0.67	1.00 (0.77; 1.30)	0.96 (0.62; 1.50)	0.92 (0.41; 2.06)	1.15 (0.30; 4.34)
0.8	1.03 (0.79; 1.33)	0.98 (0.63; 1.54)	0.95 (0.42; 2.14)	1.18 (0.32; 4.37)
0.91	1.04 (0.80; 1.36)	1.00 (0.64; 1.57)	0.96 (0.43; 2.17)	1.18 (0.32; 4.40)
0.95	1.06 (0.81; 1.37)	1.01 (0.64; 1.57)	0.97 (0.43; 2.18)	1.19 (0.32; 4.42)
1	1.06 (0.82; 1.38)	1.01 (0.65; 1.58)	0.97 (0.43; 2.18)	1.19 (0.32; 4.42)
1.05	1.07 (0.83; 1.39)	1.02 (0.66; 1.59)	0.99 (0.44; 2.21)	1.19 (0.32; 4.42)
1.1	1.08 (0.83; 1.40)	1.03 (0.66; 1.60)	0.99 (0.44; 2.21)	1.20 (0.32; 4.50)
1.25	1.10 (0.85; 1.43)	1.06 (0.68; 1.63)	1.01 (0.45; 2.23)	1.22 (0.33; 4.61)
1.5	1.15 (0.88; 1.50)	1.10 (0.71; 1.70)	1.04 (0.47; 2.31)	1.26 (0.33; 4.78)
2	1.23 (0.95; 1.60)	1.19 (0.76; 1.84)	1.09 (0.49; 2.42)	1.38 (0.36; 5.25)
3	1.38 (1.06; 1.79)	1.35 (0.87; 2.09)	1.23 (0.54; 2.76)	1.55 (0.42; 5.67)
4	1.51 (1.17; 1.95)	1.49 (0.97; 2.30)	1.38 (0.63; 3.00)	1.69 (0.45; 6.41)
5	1.64 (1.27; 2.11)	1.66 (1.08; 2.55)	1.52 (0.71; 3.28)	1.81 (0.49; 6.65)
8	1.92 (1.50; 2.45)	2.09 (1.36; 3.20)	2.03 (0.93; 4.43)	2.36 (0.64; 8.65)
10	2.08 (1.63; 2.65)	2.32 (1.51; 3.56)	2.30 (1.07; 4.96)	2.74 (0.77; 9.72)

MNAR multiple imputation: In the No Beta-blocker arm, missing observations were imputed from the observed odds of bad outcome in that arm, while in the Beta-blocker arm, missing observations were imputed from the observed odds times the Odds increase factor.

Figure S1. Randomization, treatment and follow up

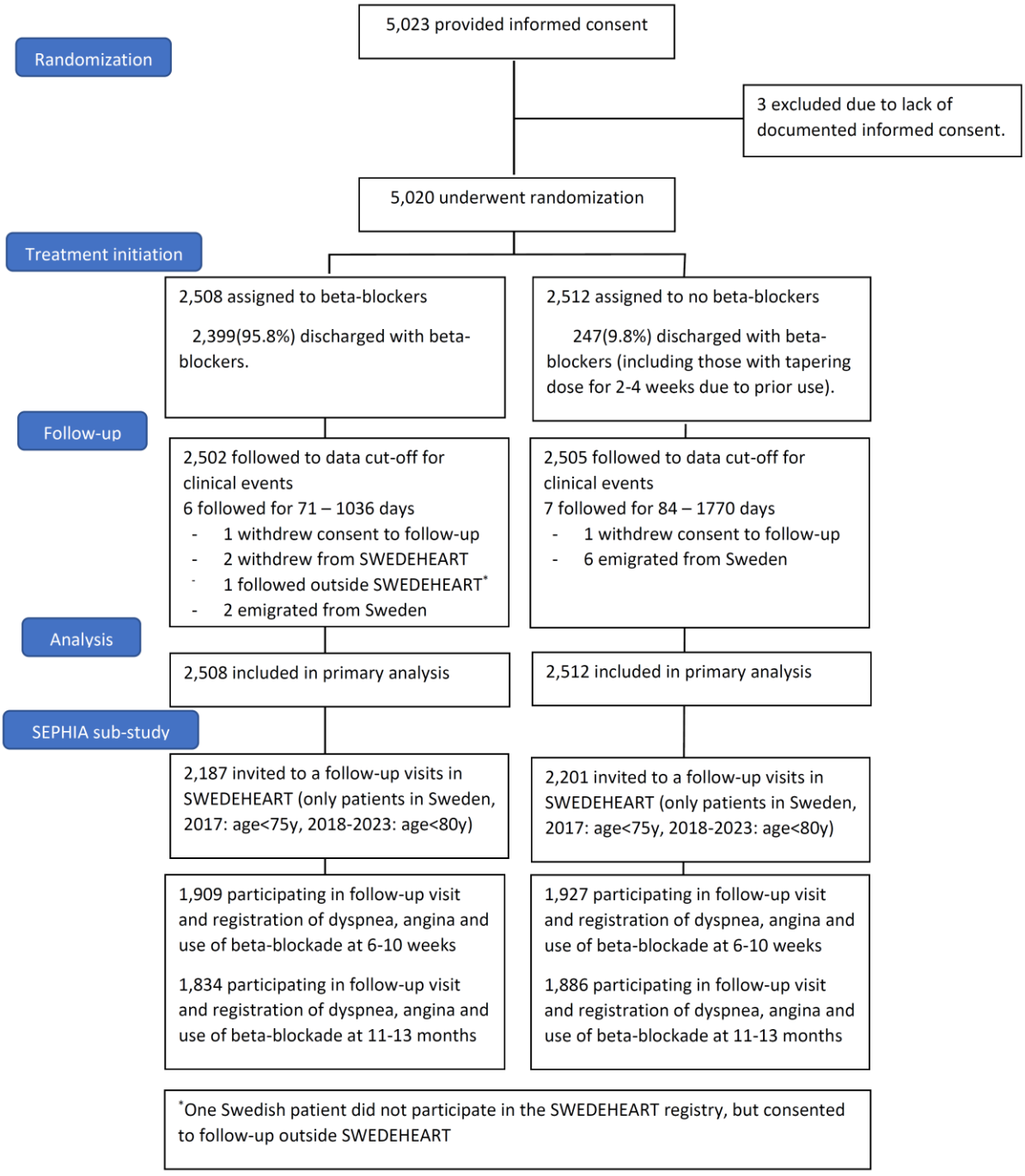


Figure S2. Cardiovascular death

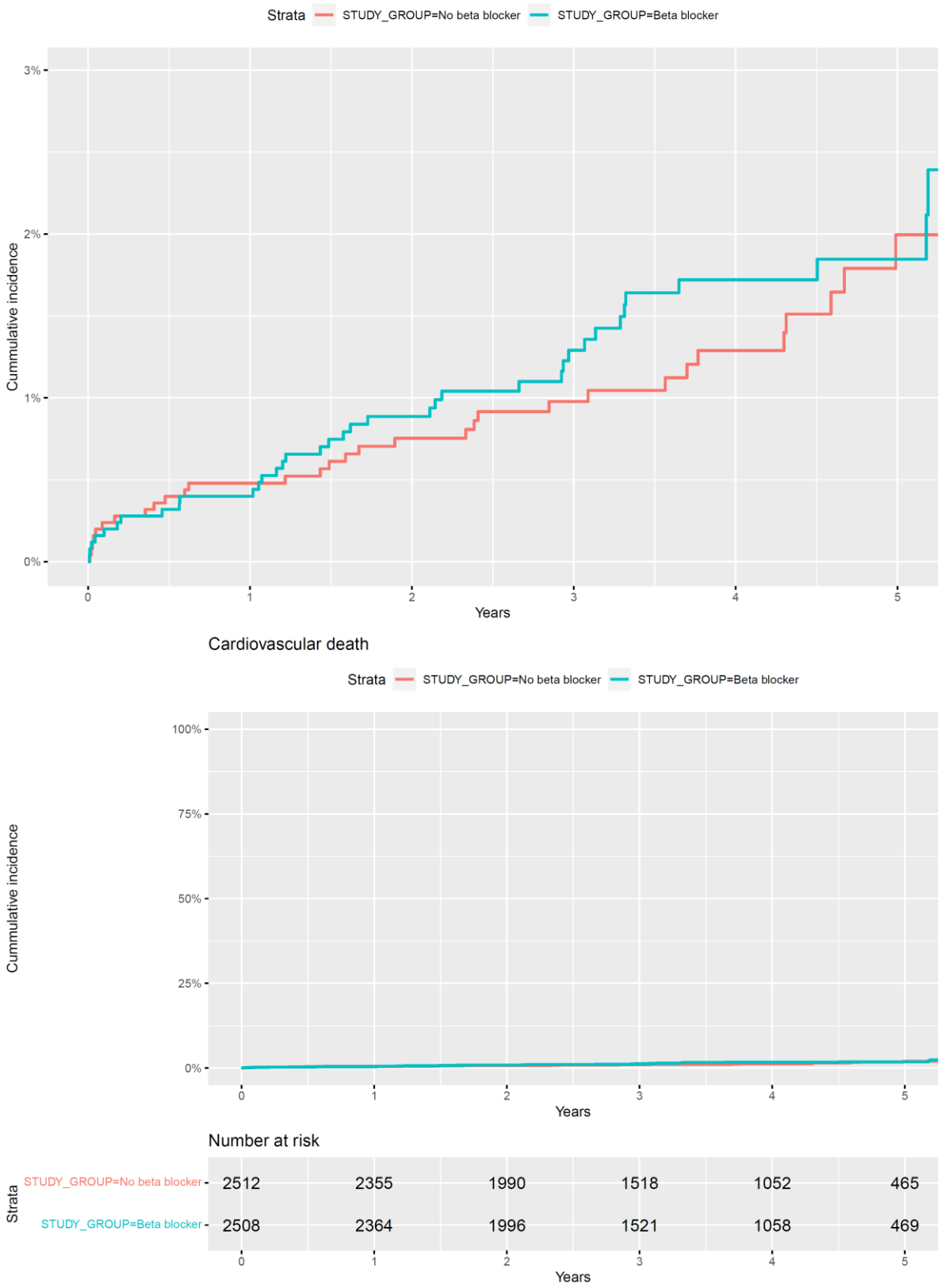


Figure S3. Admission to hospital because of atrial fibrillation

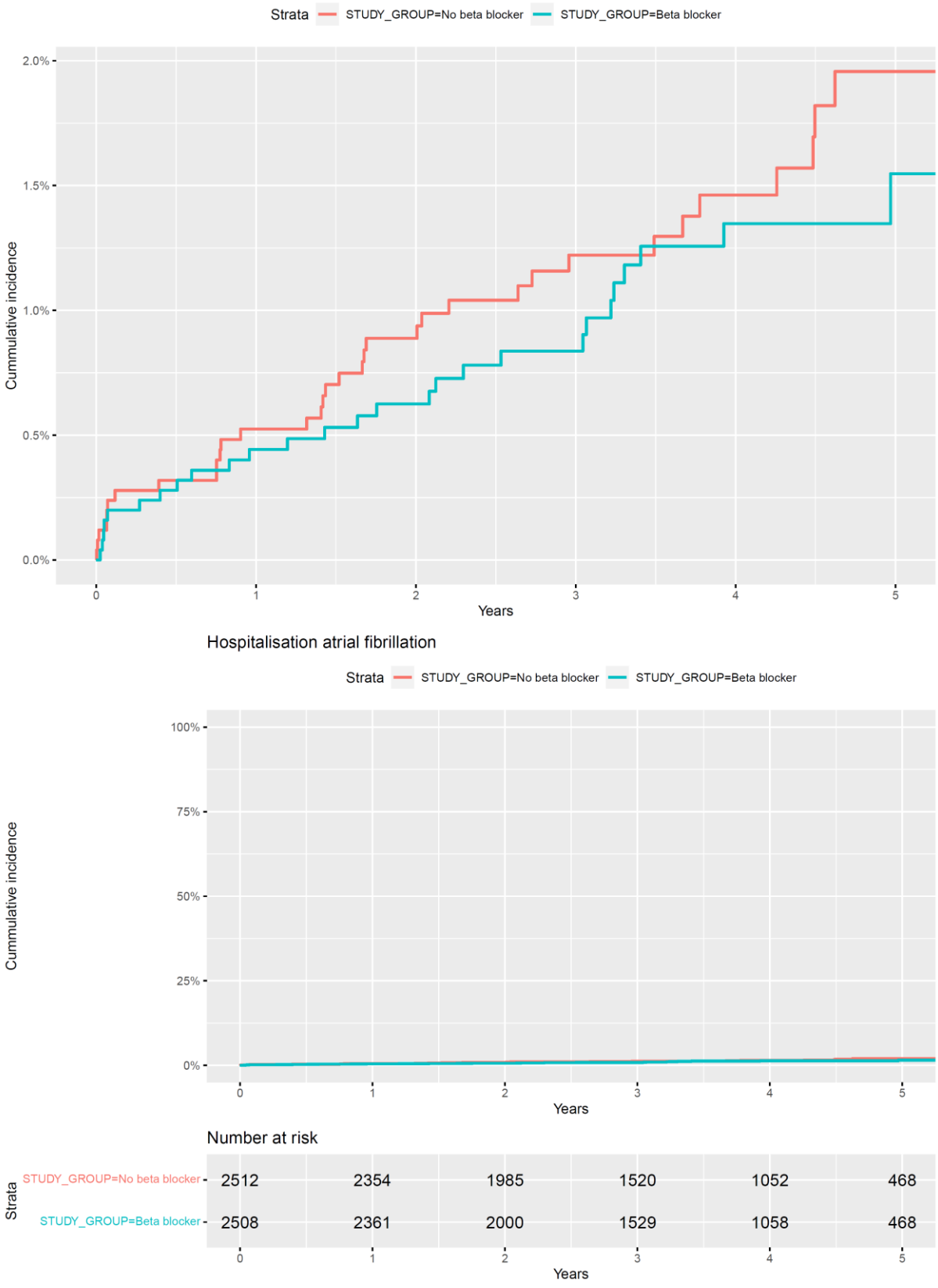


Figure S4. Admission to hospital because of heart failure

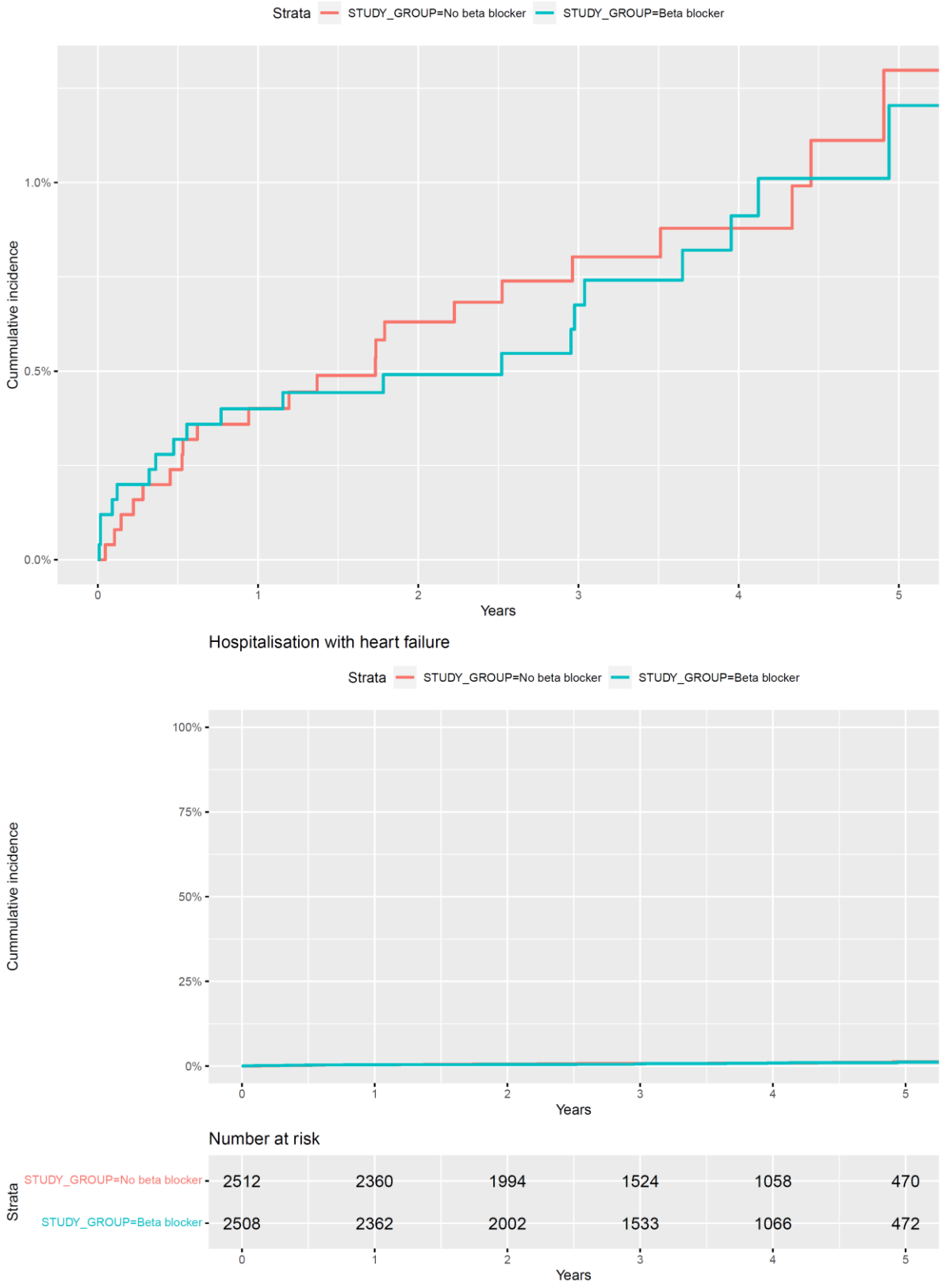


Figure S5. Hospitalization because of bradycardia, advanced AV-block (II-II), hypotension, syncope or need for pacemaker

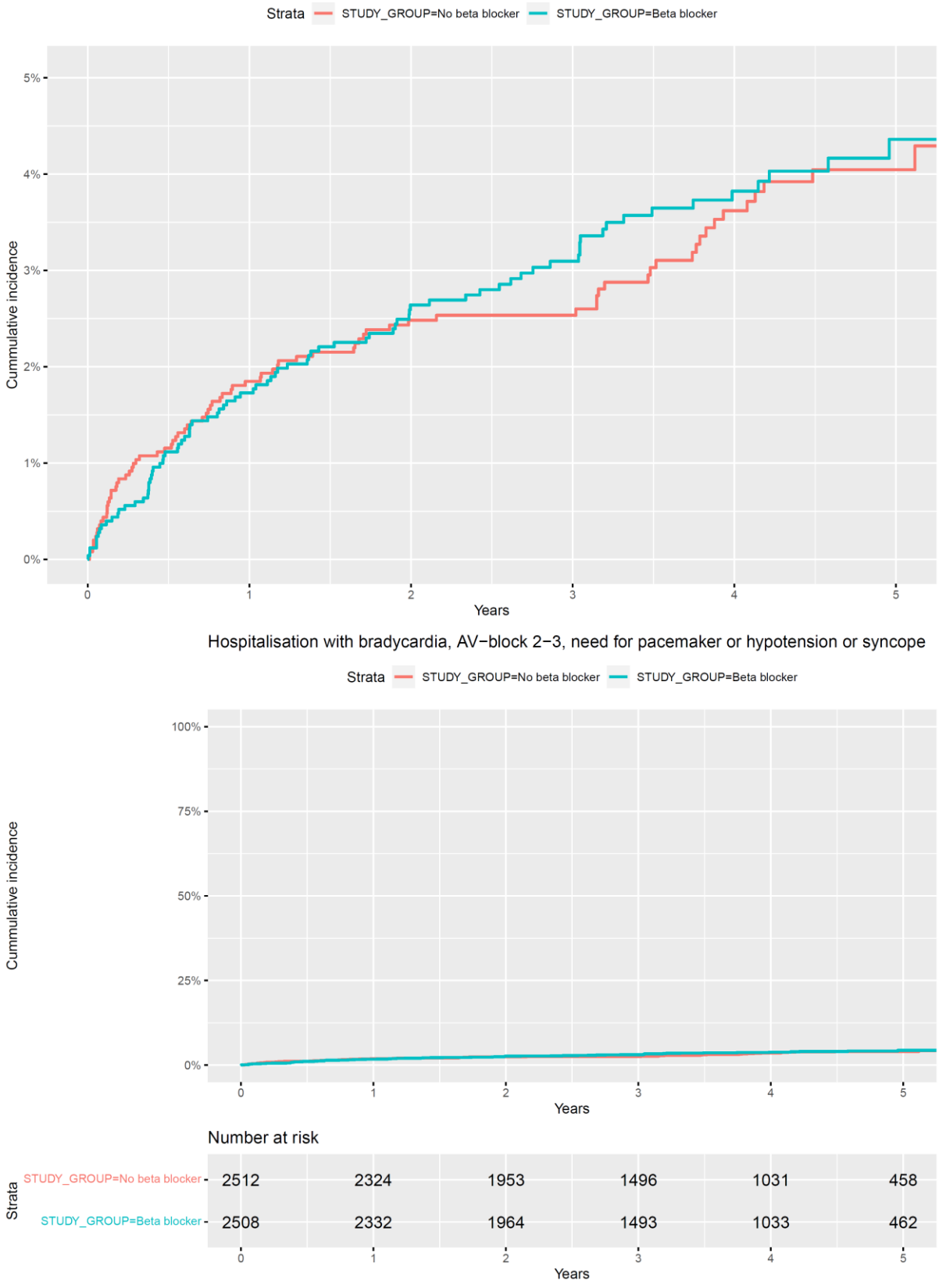


Figure S6. Hospitalization because of asthma or chronic obstructive pulmonary disease

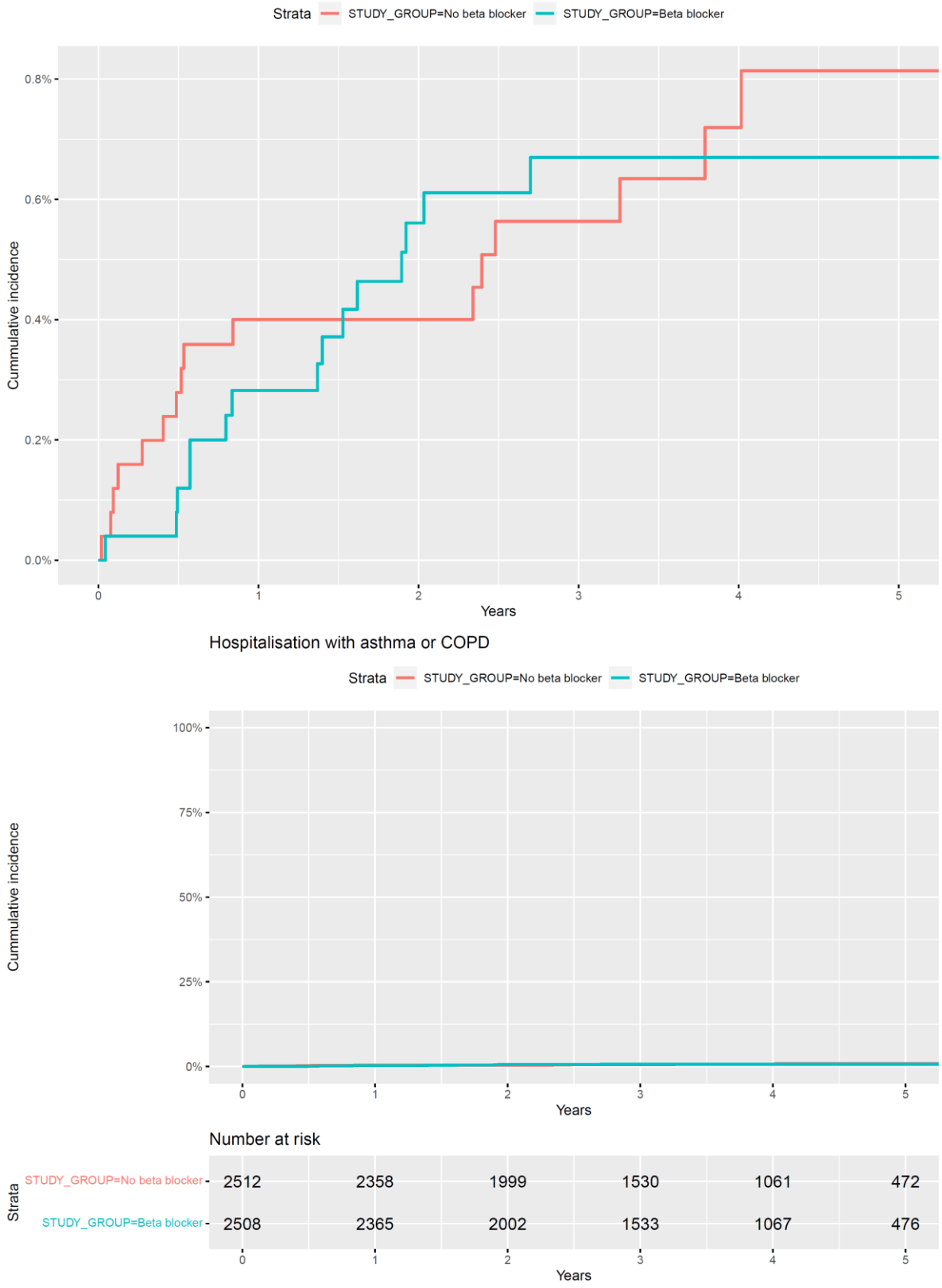


Figure S7. Hospitalization because of stroke

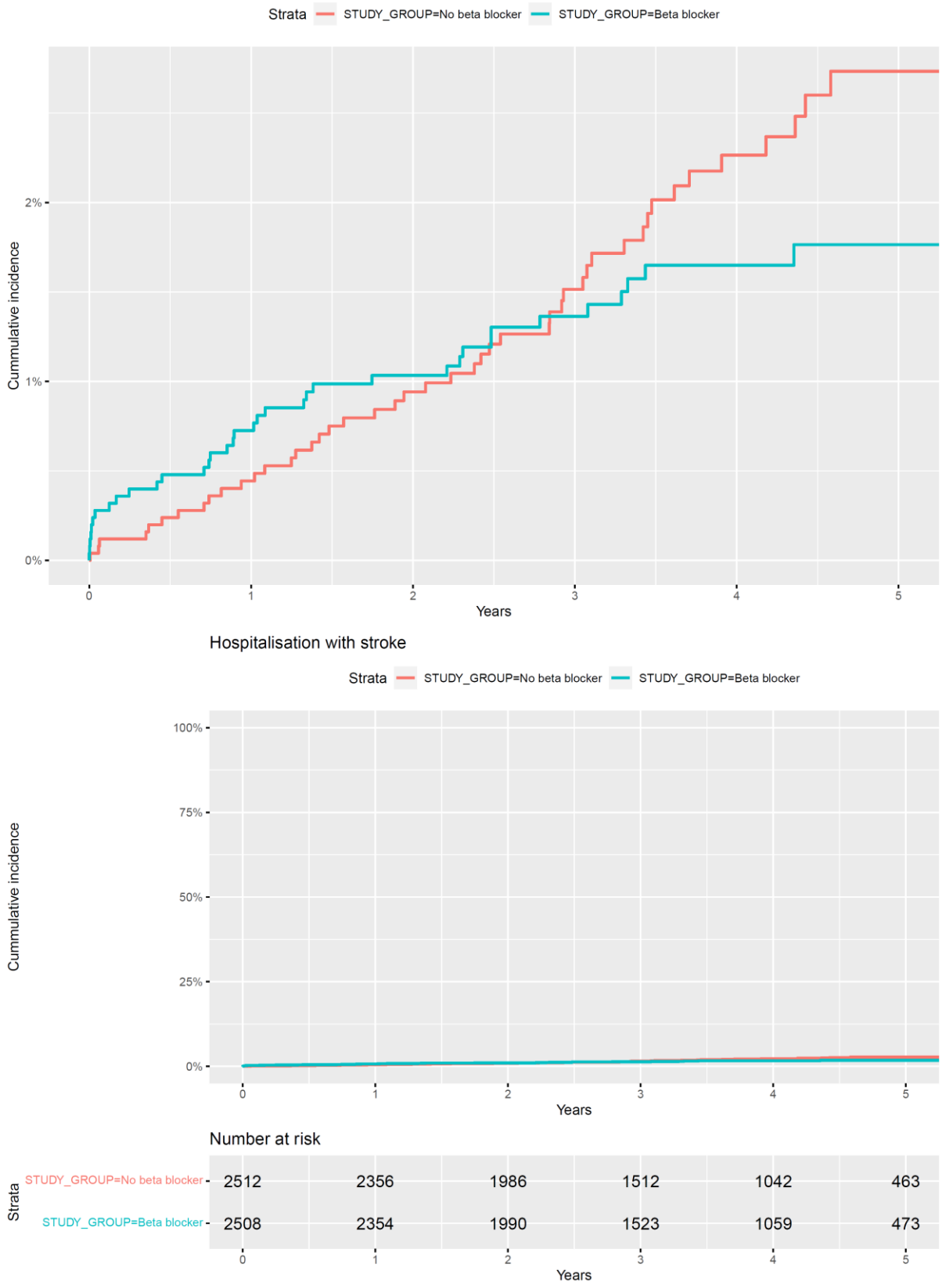
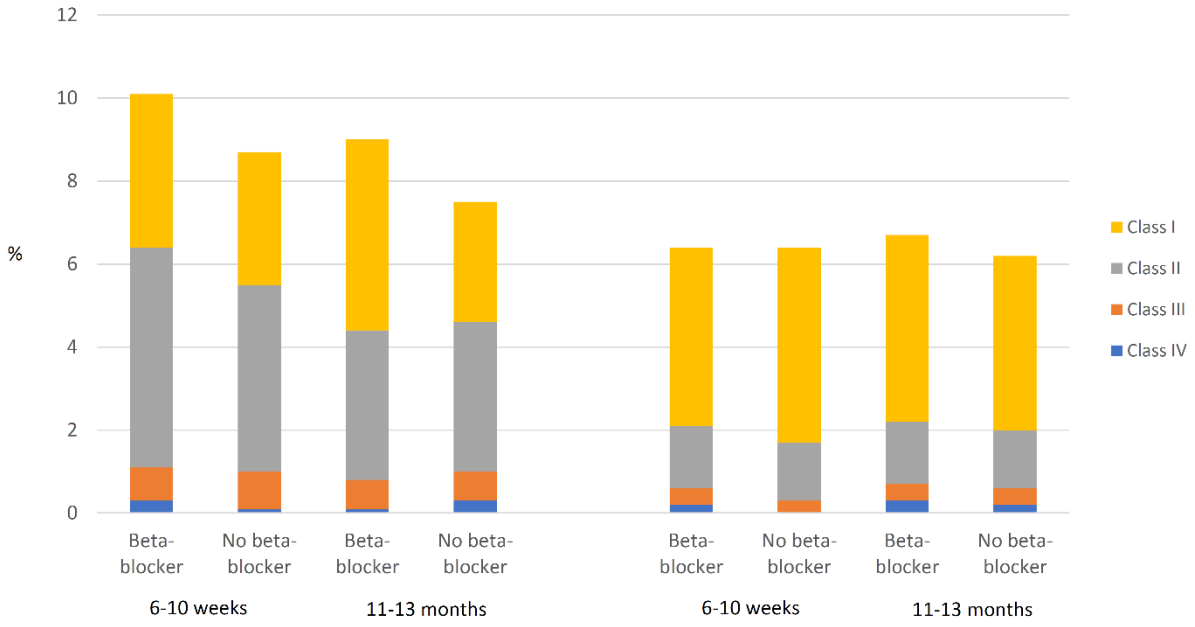
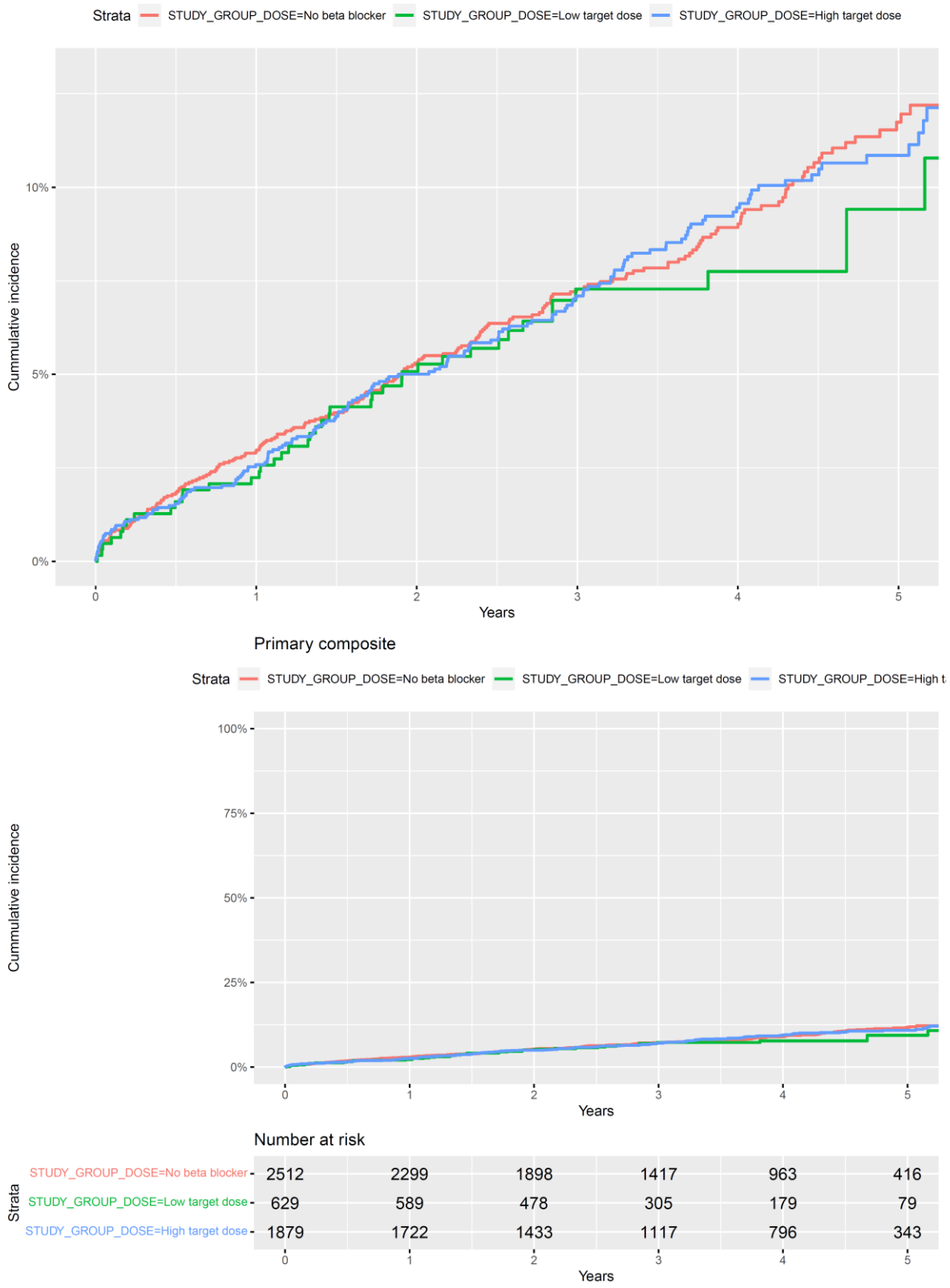


Figure S8, Dyspnea and angina pectoris after 6-10 weeks and 12-14 months



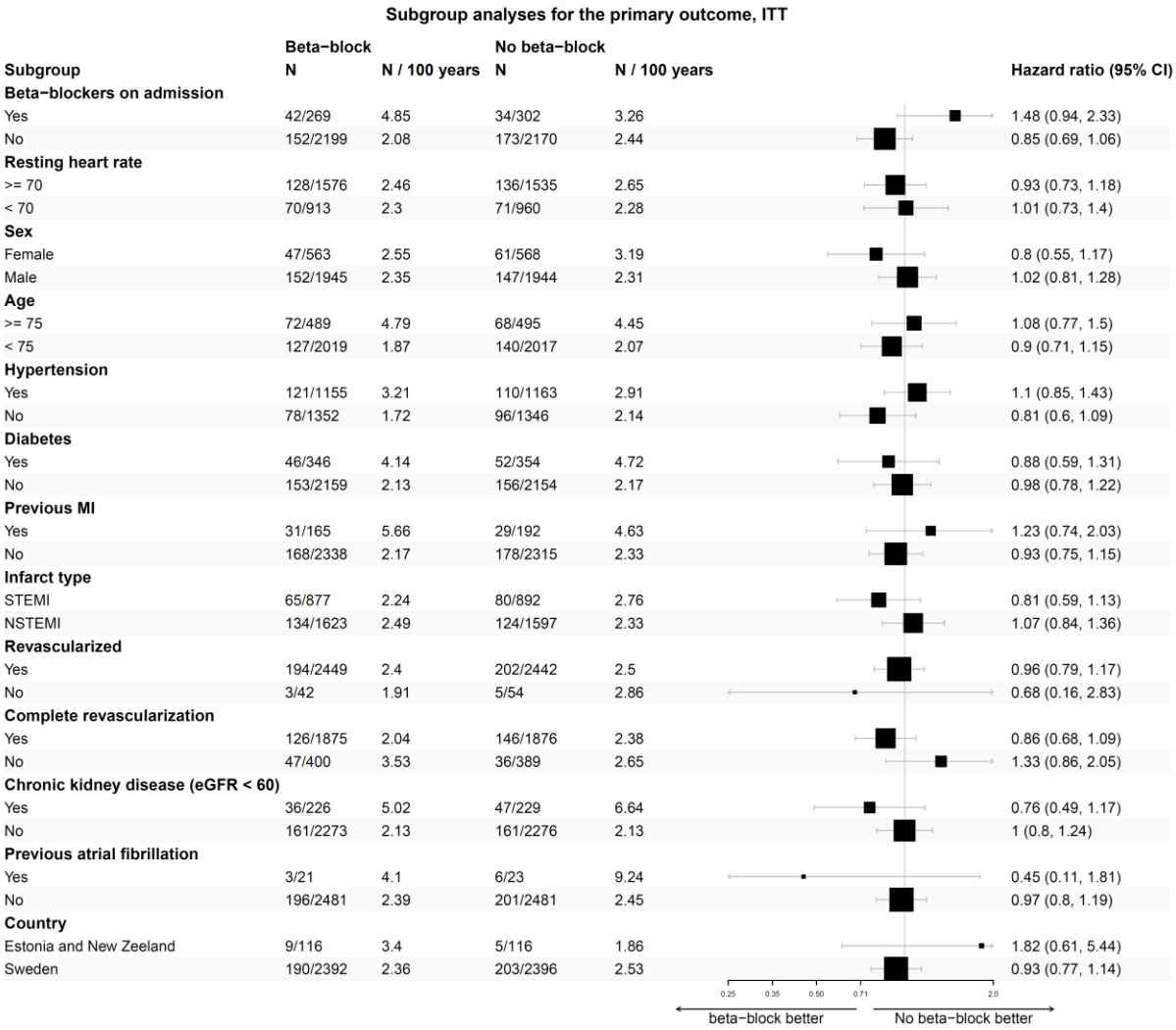
	Dyspnea				Angina			
	6-10 weeks		11-13 months		6-10 weeks		11-13 months	
	OR	**(95%CI)**	**OR**	**(95%CI)**	**OR**	**(95%CI)**	**OR**	**(95%CI)**
Proportional odds	1.18	(0.95-1.47)	1.21	(0.96-1.53)	1.01	(0.78-1.30)	1.07	(0.82-1.39)
Class I-IV vs 0	1.19	(0.95-1.48)	1.23	(0.97-1.55)	1.00	(0.77-1.30)	1.07	(0.82-1.39)
Class II-IV vs 0-I	1.17	(0.90-1.54)	0.96	(0.70-1.30)	1.24	(0.77-1.99)	1.06	(0.68-1.65)
Class III-IV vs 0-II	1.06	(0.56-2.01)	0.76	(0.37-1.51)	2.02	(0.72-6.51)	1.03	(0.46-2.32)
Class IV vs 0-III	2.53	(0.54-17.66)	0.41	(0.06-1.91)	-	-	1.29	(0.34-5.21)

Figure S9, Primary endpoint (post-hoc analysis)



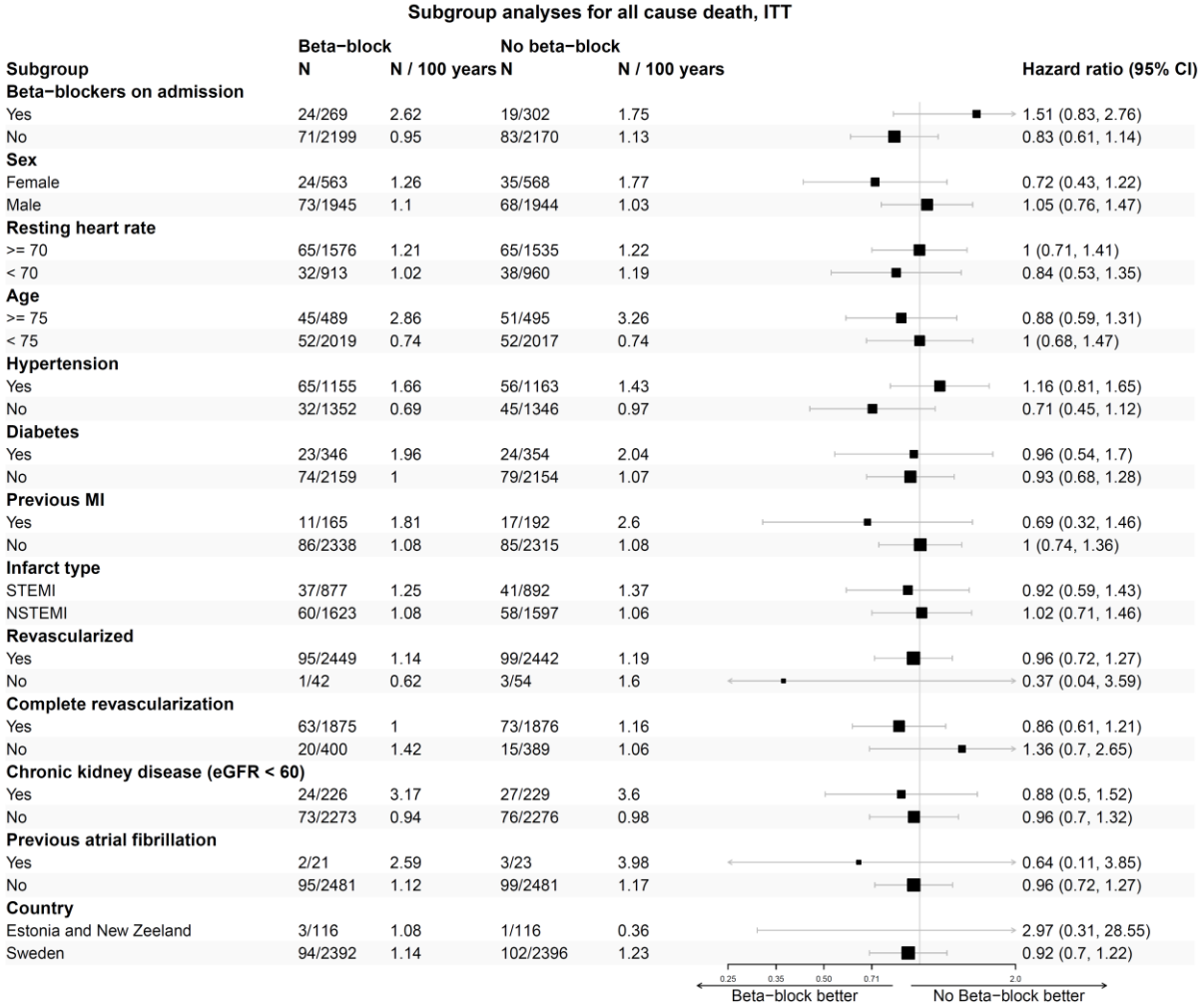
Low target dose: Less than 100 mg metoprolol or 5 mg bisoprolol
Moderate/high target dose: At least 100mg metoprolol or at least 5 mg bisoprolol

Figure S10



The subgroup based on heart rate on admission (≥70, <70) was not pre-specified in the protocol.

Figure S11



The subgroup based on heart rate on admission (≥70, <70) was not pre-specified in the protocol.

Figure S12, Non-CV death

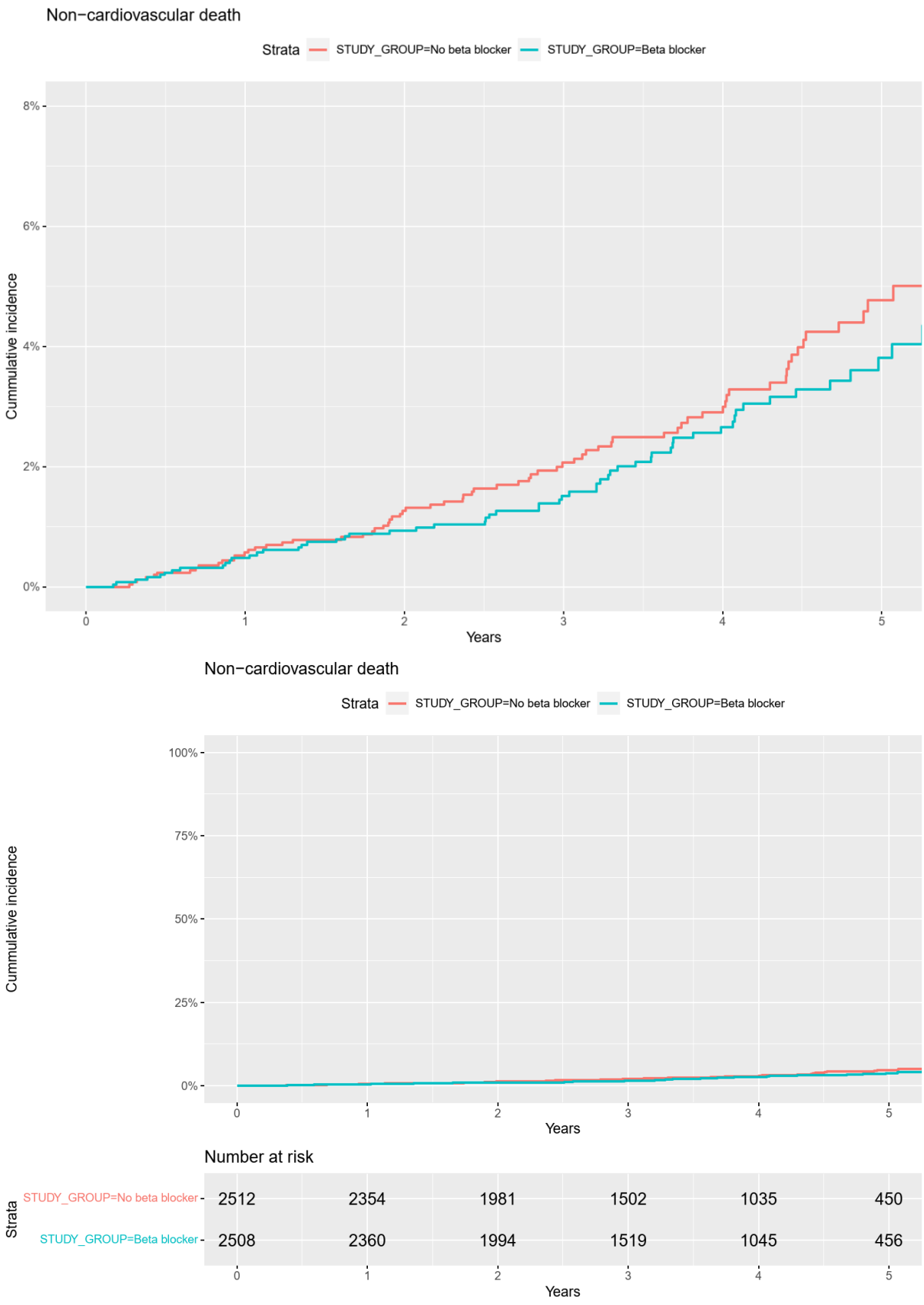
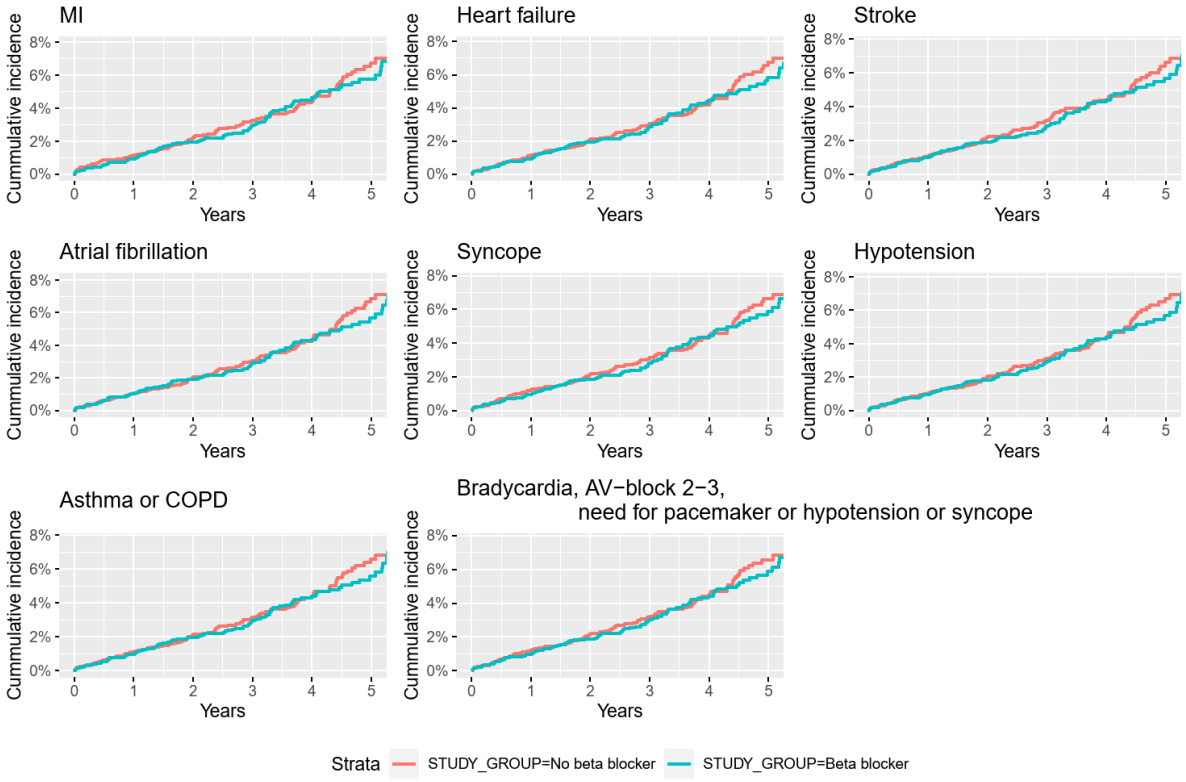


Figure S13, death before other endpoint



These cumulative incidence plots show death before the indicated endpoint, that is, death after an endpoint is not included. This description complements the cumulative incidence curve for each endpoint, which shows “endpoint before death”.

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-69.

2. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. Circulation 2015;132:302-61.