# Supplemental material

## Association of beta-blockers beyond one year after myocardial infarction and cardiovascular outcomes

**Supplementary Figure 1.** STROBE statement

**STROBE Statement** – checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| ✓ **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| ✓ **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| ✓ **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |

**Supplementary Figure 1 (continued).** STROBE statement

| | | | |
|---|---|---|---|
| ✓ | **Results** | | |
| | Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | | (b) Give reasons for non-participation at each stage |
| | | | (c) Consider use of a flow diagram |
| | Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | | (b) Indicate number of participants with missing data for each variable of interest |
| | | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| | Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| | Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | | (*b*) Report category boundaries when continuous variables were categorized |
| | | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| | Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| ✓ | **Discussion** | | |
| | Key results | 18 | Summarise key results with reference to study objectives |
| | Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| | Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| | Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| ✓ | **Other information** | | |
| | Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

## Statistical analyses software and data packages

All statistical analyses were performed at Uppsala Clinical Research Center (UCR) with the use of R version 4.2.1 (R Foundation for Statistical Computing). Following relevant R packages were utilised during the analyses:

- dplyr 1.0.10
- rms 6.3-0
- survival 3.3-1
- mice 3.14.0

**Supplementary Table 1.** Data sources and the International Code of Disease, tenth revision (ICD-10) and the Anatomical Therapeutic Chemical (ATC) codes applied to identify comorbidities and comedication

| Variable | Data source | ICD-10 / ATC code |
|---|---|---|
| Calendar year | SWEDEHEART | - |
| Age | SWEDEHEART | - |
| Sex | SWEDEHEART | - |
| Smoking | SWEDEHEART | - |
| Hypertension | SWEDEHEART, NPR | I10, I11, I12, I13, I15 |
| Diabetes mellitus | SWEDEHEART, NPR | E10, E11, E12, E13, E14 |
| Atrial fibrillation/flutter | SWEDEHEART, NPR | I48 |
| Previous MI | SWEDEHEART, NPR | I21, I22, I252 |
| Previous PCI | SWEDEHEART, NPR | Z951 |
| Previous CABG | SWEDEHEART, NPR | Z955 |
| Heart failure | SWEDEHEART, NPR | I42, I50, I110, I255, I130, I132, K761 |
| Cerebrovascular disease | SWEDEHEART, NPR | I60, I61, I63, I64, I672, I678, I679, G45 |
| Peripheral arterial disease | NPR | I70, I71, I72, I73 |
| COPD | NPR | J43, J44 |
| Asthma | NPR | J45, J46 |
| Type of MI | SWEDEHEART | - |
| Creatinine/eGFR | SWEDEHEART | - |
| Blood pressure | SWEDEHEART | - |
| In-hospital PCI | SWEDEHEART | - |
| In-hospital CABG | SWEDEHEART | - |
| Left ventricular ejection fraction | SWEDEHEART | - |
| Beta-blockers | Prescribed Drug Register | C07 |
| Acetylsalicylic acid | Prescribed Drug Register | B01AC06 |
| $P2Y_{12}$ inhibitor | Prescribed Drug Register | B01AC04, B01AC05, B01AC22, B01AC24 |
| Oral anticoagulants | Prescribed Drug Register | B01AA03, B01AE07, B01AF |
| ACE inhibitors | Prescribed Drug Register | C09A, C09B |
| ARB | Prescribed Drug Register | C09C, C09D |
| Statins | Prescribed Drug Register | C10AA |
| Diuretics | Prescribed Drug Register | C03C |

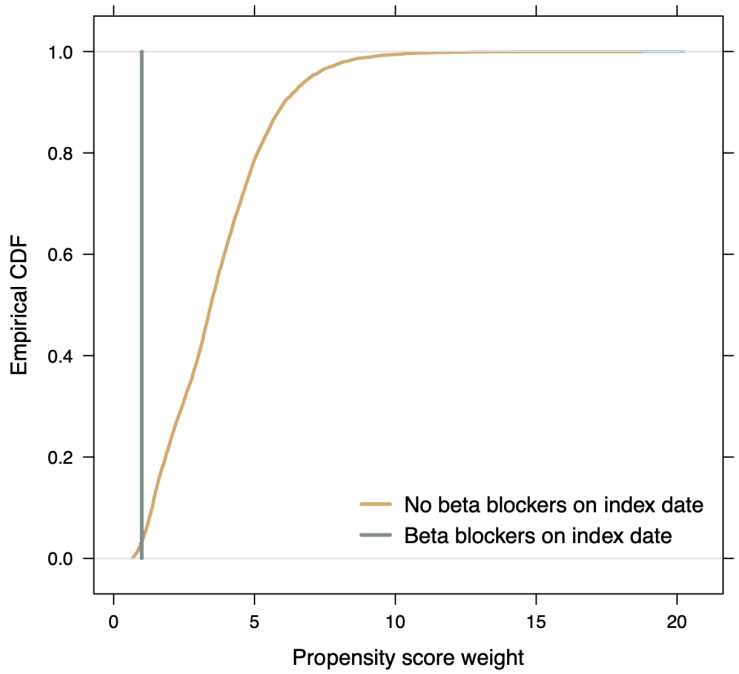
eGFR levels are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MI, myocardial infarction; NPR, National Patient Register; OAC, oral anticoagulants; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; TTR, time in therapeutic range.

**Supplementary Table 2.** Data sources and the International Code of Disease, tenth revision (ICD-10) codes applied to identify outcomes

| Variable | Data source | ICD-10 code |
|---|---|---|
| Primary composite outcome | | |
| All-cause mortality | Population register | - |
| Myocardial infarction | NPR | I21, I22 |
| Unscheduled revascularisation | SWEDEHEART | - |
| Heart failure hospitalisation | NPR | I42, I50, I110, I255, I130, I132, K761 |
| Secondary outcomes | | |
| Cardiovascular mortality | Cause of death register | I00 – I99 |
| Stroke | NPR | I60, I61, I63, I64 |
| Negative control outcome | | |
| Pneumonia | NPR | J12, J13, J14, J15, J16, J17, J18 |

Abbreviations: NPR, National Patient Register.

**Supplementary Figure 2.** Empirical cumulative distribution function plot illustrating the weights in the inverse propensity score weighting model

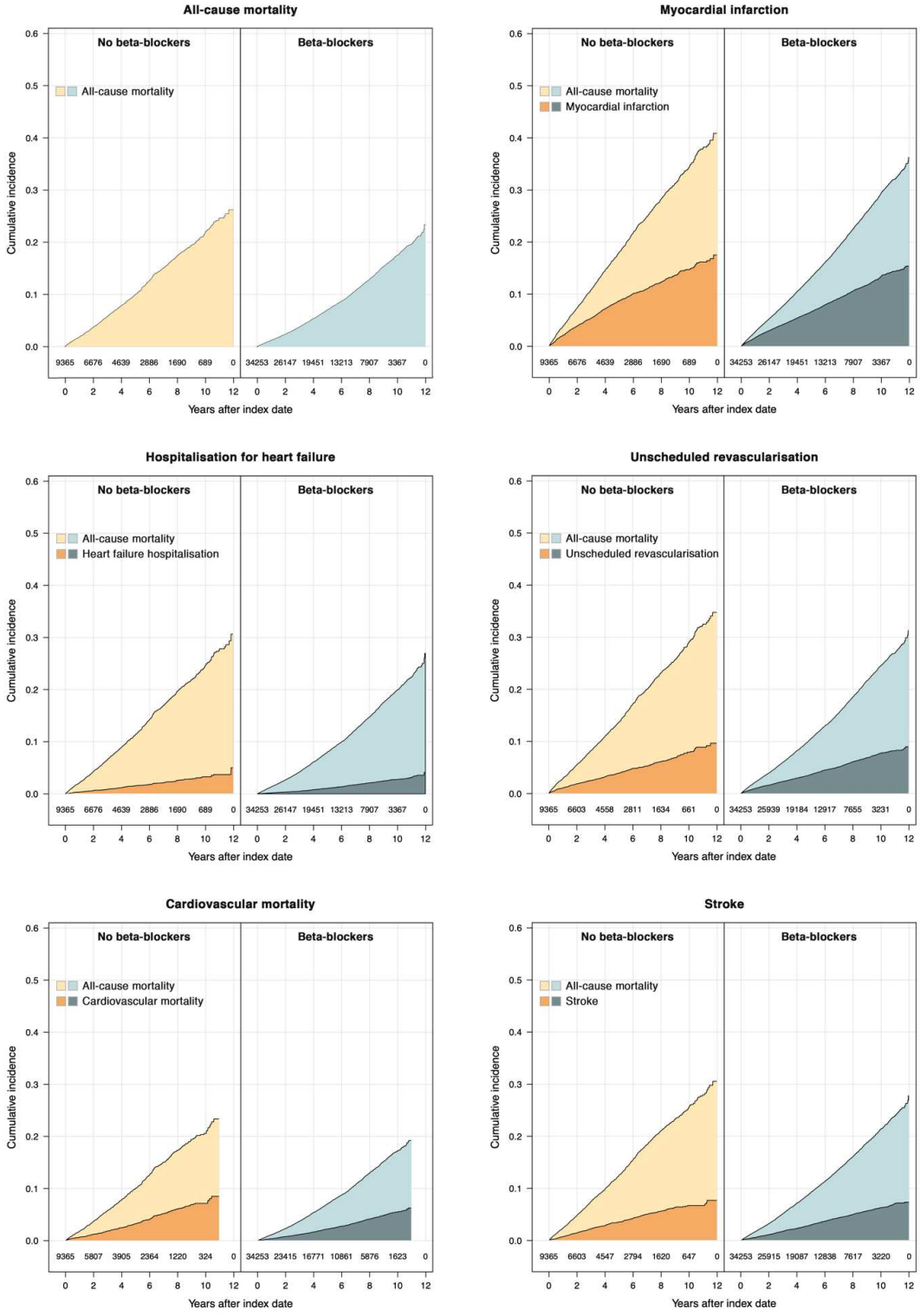


**Supplementary Table 3.** Demographics and characteristics before propensity score weighting

| Characteristic | Beta-blockers (n = 34900) | No beta-blockers (n = 11604) |
|---|---|---|
| Demographics | | |
| Age, years, median (IQR) | 64 (56 – 71) | 65 (56 – 74) |
| Sex, female, n (%) | 8871 (25.4) | 3181 (27.4) |
| Smoking, n (%) | 10973 (31.9) [516] | 3299 (29.3) [340] |
| Medical history 1 year after MI, n (%) | | |
| Hypertension | 13455 (38.6) | 4250 (36.6) |
| Diabetes mellitus | 4694 (13.4) | 1380 (11.9) |
| Atrial fibrillation/flutter | 2347 (6.7) | 765 (6.6) |
| Prior MI | 1626 (4.7) | 1083 (9.3) |
| Prior PCI | 966 (2.8) | 746 (6.4) |
| Prior CABG | 458 (1.3) | 327 (2.8) |
| Cerebrovascular disease | 1833 (5.3) | 814 (7.0) |
| Peripheral vascular disease | 854 (2.4) | 404 (3.5) |
| COPD | 997 (2.9) | 484 (4.2) |
| Index event, n (%) | | |
| NSTEMI | 21816 (62.5) [6] | 8104 (69.9) [2] |
| STEMI | 13078 (37.5) | 3498 (30.1) |
| In-hospital course and medication at discharge | | |
| eGFR, median (IQR) | 77 (67 – 89) [1408] | 78 (67 – 90) [446] |
| PCI, n (%) | 27706 (79.4) | 7845 (67.6) |
| CABG, n (%) | 1245 (3.6) | 252 (2.2) |
| Beta-blockers, n (%) | 33344 (95.6) [28] | 6426 (55.4) [9] |
| Concomitant medication 1 year after MI, n (%) | | |
| Acetylsalicylic acid | 32595 (93.4) | 8610 (74.2) |
| $P2Y_{12}$ inhibitors | 5880 (16.8) | 1501 (12.9) |
| Oral anticoagulants | 540 (1.5) | 145 (1.2) |
| ACE inhibitors | 11541 (33.1) | 2499 (21.5) |
| ARB | 4111 (11.8) | 1181 (10.2) |
| Statins | 31164 (89.3) | 7513 (64.7) |

*History about prior MI, prior PCI and prior CABG is before hospitalisation for MI. Values are in median (interquartile range [IQR]) for continuous variables and numbers (%) for categorical variables. Numbers within square brackets indicate number of missing values. eGFR levels are based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and presented in $mL/min/1.73m^2$. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

**Supplementary Figure 3.** Unadjusted cumulative incidence plot of all secondary outcomes considering competing risk by all-cause mortality



**Supplementary Table 4.** Primary and secondary outcomes in the per-protocol analysis

| | **Beta-blockers (n = 34253)** Events/100 patient-yr (incidence rate) | **No beta-blockers (n = 9365)** Events/100 patient-yr (incidence rate) | **Hazard ratio (95% CI) for beta-blockers** (unadjusted) | **Hazard ratio (95% CI) for beta-blockers** (adjusted) |
|---|---|---|---|---|
| Primary composite outcome | 1856 / 541 (3.4) | 1427 / 296 (4.8) | 0.72 (0.67 – 0.78) | 0.98 (0.90 – 1.06) |
| All-cause mortality | 772 / 544 (1.4) | 678 / 298 (2.3) | 0.70 (0.62 – 0.78) | 1.01 (0.90 – 1.14) |
| Myocardial infarction | 801 / 544 (1.5) | 567 / 298 (1.9) | 0.73 (0.65 – 0.82) | 0.95 (0.84 – 1.07) |
| Unscheduled revascularisation | 418 / 541 (0.8) | 250 / 296 (0.9) | 0.84 (0.72 – 0.99) | 0.88 (0.74 – 1.06) |
| Heart failure hospitalisation | 104 / 544 (0.2) | 80 / 298 (0.3) | 0.72 (0.53 – 0.98) | 0.91 (0.64 – 1.27) |
| Other secondary outcomes | | | | |
| Cardiovascular mortality | 271 / 495 (0.6) | 200 / 255 (0.8) | 0.78 (0.65 – 0.95) | 1.10 (0.89 – 1.36) |
| Stroke | 342 / 540 (0.6) | 228 / 294 (0.8) | 0.84 (0.70 – 1.00) | 1.01 (0.84 – 1.22) |
| Negative control outcome | | | | |
| Pneumonia | 385 / 540 (0.7) | 254 / 294 (0.9) | 0.88 (0.74 – 1.04) | 1.09 (0.91 – 1.31) |

The primary composite outcome was a composite of all-cause mortality, myocardial infarction, hospitalisation for heart failure or unscheduled coronary revascularisation. Person time and incidence rate is given in 100 person-years. Hazard ratios are given with 95% confidence intervals. The no beta-blockers group is the reference group. In the per-protocol analysis, treatment with beta-blockers is defined as a time-varying variable and patients are censored at their first treatment switch (regardless of direction). In total, 8401 (24.5%) of the patients in the beta-blockers group and 6441 (68.8%) of the patients in the no beta-blockers group did not switch treatment during follow-up for the primary composite outcome.

**Supplementary Table 5.** Primary composite outcome for subgroups in the per-protocol analysis

| | **Beta-blockers (n = 34253)** Events/100 patient-yr (incidence rate) | **No beta-blockers (n = 9365)** Events/100 patient-yr (incidence rate) | **Hazard ratio (95% CI) for beta-blockers** (unadjusted) | **Hazard ratio (95% CI) for beta-blockers** (adjusted) |
|---|---|---|---|---|
| All patients | 1856 / 541 (3.4) | 1427 / 296 (4.8) | 0.72 (0.67 – 0.78) | 0.98 (0.90 – 1.06) |
| Admission year | | | | |
| 2005 – 2010 | 1176 / 323 (3.6) | 933 / 188 (5.0) | 0.75 (0.68 – 0.82) | 1.00 (0.90 – 1.10) |
| 2011 – 2016 | 680 / 219 (3.1) | 494 / 108 (4.6) | 0.67 (0.59 – 0.75) | 0.94 (0.82 – 1.07) |
| Age | | | | |
| Age <65 years | 583 / 292 (2.0) | 407 / 155 (2.6) | 0.76 (0.67 – 0.87) | 0.77 (0.66 – 0.89) |
| Age ≥65 years | 1273 / 249 (5.1) | 1020 / 140 (7.3) | 0.73 (0.67 – 0.80) | 1.06 (0.96 – 1.16) |
| Sex | | | | |
| Female | 544 / 134 (4.1) | 423 / 78 (5.4) | 0.78 (0.68 – 0.89) | 0.96 (0.83 – 1.11) |
| Male | 1004 / 217 (4.6) | 1312 / 407 (3.2) | 0.70 (0.64 – 0.76) | 0.97 (0.88 – 1.07) |
| Hypertension | | | | |
| Yes | 784 / 194 (4.1) | 570 / 93 (6.2) | 0.67 (0.60 – 0.75) | 1.03 (0.91 – 1.17) |
| No | 1072 / 348 (3.1) | 857 / 203 (4.2) | 0.75 (0.68 – 0.82) | 0.92 (0.83 – 1.02) |
| Diabetes mellitus | | | | |
| Yes | 328 / 64 (5.2) | 233 / 30 (7.9) | 0.67 (0.56 – 0.81) | 0.94 (0.77 – 1.15) |
| No | 1528 / 478 (3.2) | 1194 / 266 (4.5) | 0.73 (0.67 – 0.79) | 0.98 (0.90 – 1.07) |
| Atrial fibrillation | | | | |
| Yes | 241 / 33 (7.4) | 157 / 15 (10.2) | 0.70 (0.57 – 0.87) | 1.11 (0.87 – 1.43) |
| No | 1615 / 508 (3.2) | 1270 / 280 (4.5) | 0.72 (0.67 – 0.78) | 0.96 (0.88 – 1.05) |
| Previous myocardial infarction | | | | |
| Yes | 163 / 18 (9.0) | 240 / 23 (10.2) | 0.82 (0.66 – 1.00) | 1.04 (0.84 – 1.29) |
| No | 1693 / 523 (3.2) | 1187 / 272 (4.4) | 0.77 (0.71 – 0.83) | 0.98 (0.90 – 1.06) |
| Type of myocardial infarction | | | | |
| NSTEMI | 1239 / 334 (3.7) | 1023 / 204 (5.0) | 0.74 (0.68 – 0.81) | 0.98 (0.89 – 1.07) |
| STEMI | 614 / 207 (3.0) | 404 / 91 (4.4) | 0.70 (0.62 – 0.80) | 0.96 (0.83 – 1.12) |
| In-hospital PCI | | | | |
| Yes | 1172 / 432 (2.7) | 790 / 203 (3.9) | 0.72 (0.66 – 0.79) | 0.91 (0.82 – 1.01) |
| No | 684 / 109 (6.3) | 637 / 93 (6.9) | 0.89 (0.80 – 1.00) | 1.05 (0.93 – 1.19) |

The primary composite outcome was a composite of all-cause mortality, myocardial infarction, hospitalization for heart failure or unscheduled coronary revascularisation. Person time and incidence rate is given in 100 person-years. Hazard ratios are given with 95% confidence intervals. The no beta-blockers group is the reference group. In the per-protocol analysis, treatment with beta-blockers is defined as a time-varying variable and patients are censored at their first treatment switch (regardless of direction).