

INFORMATION ABOUT THE BleeMACS REGISTRY

1. BleeMACS DESCRIPTION

BleeMACS is a retrospective, observational, multicenter cohort study with voluntary participation by 15 centers from 10 countries (Canada, Brazil, China, Japan, Germany, Poland, Netherlands, Spain, Italy, and Greece). This is an investigator-dependent initiative to create an unfunded registry whose aim was to expand knowledge about ischemic and hemorrhagic events in the first year after hospital discharge for an acute coronary syndrome (ACS) in patients undergoing percutaneous coronary intervention (PCI). All the participating centers were university hospitals with a 24-hour catheterization laboratory, and with internal clinical registries on ACS. In each of the participating centers, consecutive ACS patients discharged in any time period between November 2003 and June 2014, with angiographically significant coronary stenosis ($\geq 50\%$ in left main coronary artery, $\geq 70\%$ in the rest of the coronary arteries) treated with PCI, were included. Only the first ACS during the study period was included. The study was registered on ClinicalTrial.gov (NCT02466854).

For the purpose of BleeMACS, a database was designed and sent to each of the 15 participating centers. In this database, information on clinical, analytical and angiographic variables was included retrospectively, as well as data related to follow-up, in terms of mortality, ischemic events, and hemorrhagic events. The completed databases from each center were sent in an encrypted format to the coordination center, the Álvaro Cunqueiro University Hospital in Vigo (Spain), where they were merged into a single registry. The analysis of this registry was carried out by 2 researchers from the coordination center. All this was done in accordance with the provisions of the Helsinki Declaration, with the registration being approved by the local ethics committees.

2. INCLUSION CRITERIA FOR THE BleeMACS REGISTRY

Consecutive patients who fulfilled all the following requirements:

1. Being consecutively discharged with diagnosis of ACS in any timeframe of the period between November 2003 and June 2014.

ACSs were classified as acute myocardial infarction (AMI) with persistent ST-segment elevation myocardial infarction (STEMI), I with non-ST-elevation acute myocardial infarction (NSTEMI) and unstable angina, based on the definitions accepted in the clinical guidelines. Diagnoses of AMI were based on the third universal definition of AMI. The diagnosis of unstable angina was established in the presence of suggestive symptoms, or objective evidence of myocardial ischemia in the stress test, together with the detection of a culprit lesion on coronary angiography.

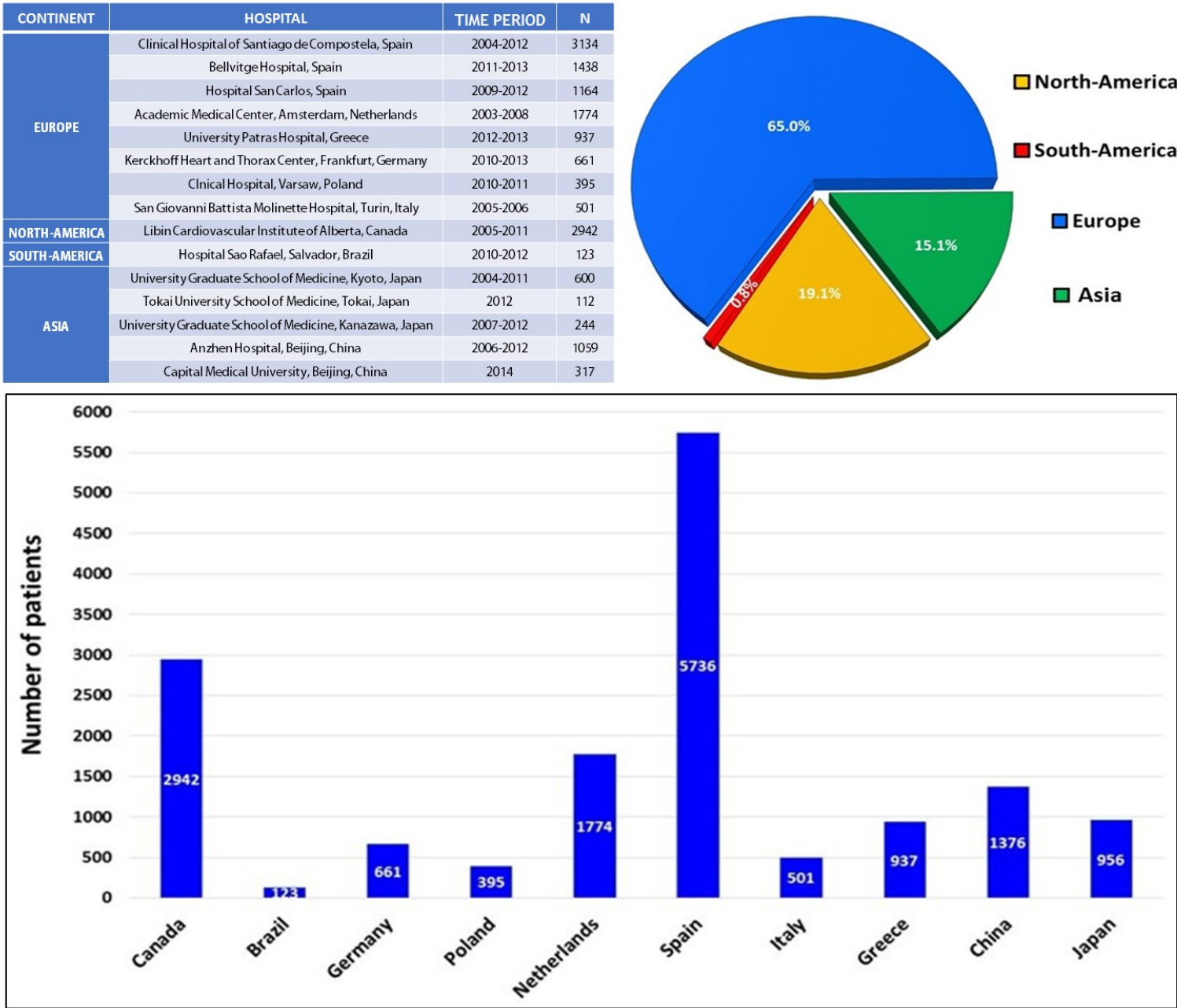
2. Having evidence of angiographically significant coronary stenosis ($\geq 50\%$ in left main coronary artery, $\geq 70\%$ in the rest of the coronary arteries) during the index entry by ACS.
3. Performance of PCI during the index entry for ACS.

3. VARIABLES INCLUDED IN THE BleeMACS REGISTRY

- Demographic variables: Date of admission (date variable), date of discharge (date variable), date of birth (date variable), age (continuous variable, years), sex (male or female).
- Baseline characteristics: Diabetes mellitus (yes/no), arterial hypertension (yes/no), dyslipidemia (yes/no), history of cancer in the last 5 years (yes/no), previous admission due to bleeding (yes/no), peripheral arterial disease (yes/no), previous ischemic stroke (yes/no), previous acute myocardial infarction (ami) (yes/no), previous percutaneous coronary intervention (yes/no), previous coronary artery by-pass graft (yes/no).
- ACS presentation: Type of ACS (unstable angina / NSTEMI / STEMI), cardiac arrest on admission (yes/no), Killip class (I / II / III / IV), creatinine on admission (continuous variable, mg/dL), hemoglobin on admission (continuous variable, g/dL).
- Coronary angiography and PCI: Multivessel disease (2 or more coronary arteries with stenosis \geq 70%), left coronary artery stenosis \geq 50% (yes/no), type of stent (conventional or drug-eluting stent).
- Echocardiographic data: left ventricular ejection fraction before discharge (continuous variable; %).
- In-hospital events: Major TIMI bleeding during admission (yes/no), AMI during admission (yes/no; elevation of TPI +/- clinical angina or ECG ischemic changes), heart failure during admission (yes/no).
- Medical therapy at discharge: Aspirin (yes/no), clopidogrel (yes/no), ticagrelor (yes/no), prasugrel (yes/no), oral anticoagulation (yes/no), beta-blocker (yes/no), ACEI/ARB (yes/no), statins (yes/no).
- 1-year follow-up: Death (yes/no), date of death (date variable), hospital admission by bleeding during follow-up (yes/no), date of bleeding (date variable), reinfarction during follow-up (yes/no), date of reinfarction (date variable).

Figure 1

Distribution of patients in the BleeMACS Registry by centers, countries, and continents.



Correcciones a la Figura

North-America → North America

South-America → South America

UNIVARIATE COX ANALYSIS

Table 1

Univariate Cox analysis for 1-year all-cause death after multiple imputation for missing values

| Variables | HR | 95% CI | <i>P</i> |
|------------------------------------|------|-----------|----------|
| <i>Age, per 1 y</i> | 1.07 | 1.06-1.08 | < .001 |
| <i>Female sex</i> | 1.59 | 1.33-1.89 | < .001 |
| <i>Region</i> | | | |
| Europe | Ref | Ref | Ref |
| America | 0.31 | 0.23-0.42 | < .001 |
| Asia | 0.69 | 0.54-0.88 | .003 |
| <i>Year</i> | | | |
| 2003-2006 | Ref | Ref | Ref |
| 2007-2010 | 0.81 | 0.65-0.99 | .043 |
| 2011-2015 | 0.97 | 0.78-1.20 | .769 |
| <i>Diabetes mellitus</i> | 2.19 | 1.85-2.59 | < .001 |
| <i>Hypertension</i> | 1.47 | 1.24-1.76 | < .001 |
| <i>Dyslipidemia</i> | 0.71 | 0.60-0.84 | < .001 |
| <i>Peripheral artery disease</i> | 3.43 | 2.76-4.27 | < .001 |
| <i>Prior myocardial infarction</i> | 1.52 | 1.23-1.90 | < .001 |
| <i>Prior heart failure</i> | 3.40 | 2.56-4.52 | < .001 |
| <i>Prior stroke</i> | 2.65 | 2.09-3.37 | < .001 |

| | | | |
|---|------|-----------|--------|
| <i>Known malignant disease</i> | 3.83 | 3.11-4.72 | < .001 |
| <i>Unstable angina</i> | 0.59 | 0.44-0.80 | .001 |
| <i>ST-segment elevation myocardial infarction</i> | 0.96 | 0.82-1.14 | .661 |
| <i>Killip \geq II</i> | 3.67 | 3.08-4.38 | < .001 |
| <i>Left ventricular ejection fraction \leq 40%</i> | 2.28 | 1.88-2.78 | < .001 |
| <i>Hemoglobin at admission, per 1 g/dL</i> | 0.71 | 0.68-0.74 | < .001 |
| <i>Creatinine at admission, per 1 mg/dL</i> | 1.48 | 1.39-1.56 | < .001 |
| <i>Multivessel coronary disease</i> | 1.64 | 1.37-1.98 | < .001 |
| <i>Drug-eluting stent</i> | 0.72 | 0.60-0.86 | < .001 |
| <i>Complete revascularization</i> | 0.63 | 0.53-0.75 | < .001 |
| <i>In-hospital reinfarction</i> | 2.43 | 1.50-3.94 | < .001 |
| <i>In-hospital heart failure</i> | 3.27 | 2.53-4.21 | < .001 |
| <i>Dual antiplatelet therapy</i> | 0.60 | 0.45-0.80 | < .001 |
| <i>Oral anticoagulation</i> | 2.28 | 1.74-2.98 | < .001 |
| <i>Beta-blockers</i> | 0.40 | 0.34-0.48 | < .001 |
| <i>Statins</i> | 0.29 | 0.24-0.36 | < .001 |
| <i>ACEI/ARB</i> | 0.62 | 0.52-0.73 | < .001 |

ACEI/ARB, angiotensin converting-enzyme inhibitors/angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio.

PROPENSITY SCORE ANALYSIS

Propensity scores were estimated using a nonparsimonious multivariate logistic regression model, with angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) therapy as the dependent variables and those characteristics that differed between patients treated and not treated with beta-blockers as covariates (age, sex, year of admission, country, diabetes, hypertension, dyslipidemia, peripheral artery disease, prior myocardial infarction, prior heart failure, prior stroke, history of cancer, unstable angina, ST-segment elevation myocardial infarction, Killip class, left ventricular ejection fraction, creatinine at admission, hemoglobin at admission, multivessel coronary artery disease, drug-eluting stent, complete revascularization, in-hospital heart failure, in-hospital reinfarction, dual antiplatelet therapy, oral anticoagulation, beta-blockers, statins). The area under the curve for the propensity score model was 0.70 (95% CI 0.69-0.71), which indicated an adequate discrimination for the model.

A subsequent PS matching was performed to assemble a cohort in which all the measured covariates would be well balanced across the comparator group. Matching was performed using the PS matching algorithm in SPSS 24.0 (based on R 3.2.2), with 1:1 nearest-neighbor matching without replacement and with a caliper width of 0.1 of the standard deviation of all PSs. Standard mean differences were estimated for all covariates before and after matching to assess prematching imbalance and postmatching balance; standardized mean differences of < 10% for a given covariate indicate adequate balance. In the PS-matched population, continuous variables were compared with a 2-way analysis of variance or the median regression test, as appropriate; categorical variables were compared using McNemar tests.

For the PS matching after multiple imputation, we averaged the m propensity scores for each record across the completed datasets, and performed PS matching with these averaged scores to estimate the treatment effect. We also estimated the impact of ACEI/ARB using PS matching within each completed data set.

Table 2

Detailed balance of propensity score matching

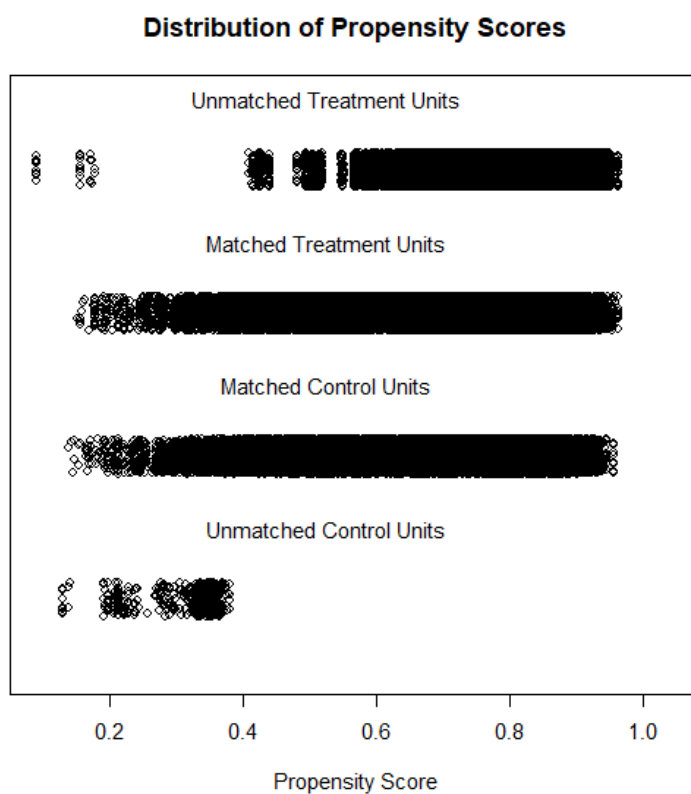
| Subsample | | Means treated | | Means control | | SD control | | Std. mean diff. | |
|-------------|--|---------------|----------|---------------|--------|------------|--------|-----------------|--------|
| s | Covariates | Before | After | Before | Before | After | After | Before | After |
| (all cases) | propensity | 0.776 | 0.697 | 0.678 | 0.812 | 0.108 | 0.148 | 0.812 | 0.108 |
| | Age | 63.688 | 63.263 | 63.490 | 0.016 | -0.015 | 12.944 | 0.016 | -0.015 |
| | Female sex | 0.226 | 0.250 | 0.254 | -0.067 | -0.006 | 0.435 | -0.067 | -0.006 |
| | Year | 2009.092 | 2008.208 | 2008.256 | 0.321 | -0.028 | 2.659 | 0.321 | -0.028 |
| | Country | 0.191 | 0.256 | 0.224 | -0.103 | -0.036 | 0.417 | -0.103 | -0.036 |
| | Diabetes | 0.248 | 0.221 | 0.217 | 0.073 | 0.011 | 0.412 | 0.073 | 0.011 |
| | Hypertension | 0.613 | 0.525 | 0.507 | 0.218 | 0.028 | 0.500 | 0.218 | 0.028 |
| | Dyslipidemia | 0.537 | 0.512 | 0.492 | 0.090 | 0.035 | 0.500 | 0.090 | 0.035 |
| | Peripheral artery disease | 0.059 | 0.058 | 0.059 | -0.002 | -0.001 | 0.235 | -0.002 | -0.001 |
| | Prior myocardial infarction | 0.121 | 0.115 | 0.117 | 0.012 | -0.006 | 0.321 | 0.012 | -0.006 |
| | Prior heart failure | 0.033 | 0.033 | 0.033 | 0.001 | -0.001 | 0.179 | 0.001 | -0.001 |
| | Prior stroke | 0.058 | 0.061 | 0.063 | -0.023 | -0.007 | 0.242 | -0.023 | -0.007 |
| | History of cancer | 0.057 | 0.065 | 0.070 | -0.058 | -0.015 | 0.253 | -0.058 | -0.015 |
| | Unstable angina | 0.130 | 0.143 | 0.145 | -0.045 | -0.001 | 0.350 | -0.045 | -0.001 |
| | ST-segment elevation myocardial infarction | 0.586 | 0.591 | 0.564 | 0.043 | 0.047 | 0.495 | 0.043 | 0.047 |

| | | | | | | | | |
|---------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| Killip >1 | 0.138 | 0.125 | 0.125 | 0.037 | -0.001 | 0.331 | 0.037 | -0.001 |
| Left ventricular ejection fraction | 52.398 | 53.094 | 53.538 | -0.106 | -0.037 | 10.266 | -0.106 | -0.037 |
| Creatinine | 0.941 | 0.968 | 1.003 | -0.148 | -0.064 | 0.627 | -0.148 | -0.064 |
| Hemoglobin | 14.079 | 13.956 | 13.872 | 0.118 | 0.039 | 1.790 | 0.118 | 0.039 |
| Multivessel disease | 0.490 | 0.482 | 0.483 | 0.012 | -0.003 | 0.500 | 0.012 | -0.003 |
| Drug-eluting stent | 0.397 | 0.347 | 0.377 | 0.041 | -0.064 | 0.485 | 0.041 | -0.064 |
| Complete revascularization | 0.620 | 0.587 | 0.586 | 0.070 | -0.001 | 0.492 | 0.070 | -0.001 |
| Dual antiplatelet therapy | 0.949 | 0.930 | 0.930 | 0.087 | -0.005 | 0.253 | 0.087 | -0.005 |
| Oral anticoagulation | 0.054 | 0.045 | 0.039 | 0.066 | 0.029 | 0.193 | 0.066 | 0.029 |
| Beta-blockers | 0.860 | 0.705 | 0.648 | 0.611 | 0.140 | 0.475 | 0.611 | 0.140 |
| Statins | 0.943 | 0.909 | 0.889 | 0.233 | 0.064 | 0.308 | 0.233 | 0.064 |
| In-hospital reinfarction | 0.013 | 0.014 | 0.014 | -0.006 | 0.002 | 0.116 | -0.006 | 0.002 |
| In-hospital heart failure | 0.044 | 0.041 | 0.042 | 0.009 | -0.005 | 0.201 | 0.009 | -0.005 |

SD, standard deviation; Std. mean diff., standardized mean difference.

Figure 2

Distribution of propensity scores.



Correcciones a la figura

Distribution of Propensity Scores -> Distribution of propensity scores

Unmatched Treatment Units -> Unmatched treatment units

Matched Treatment Units -> Matched treatment units

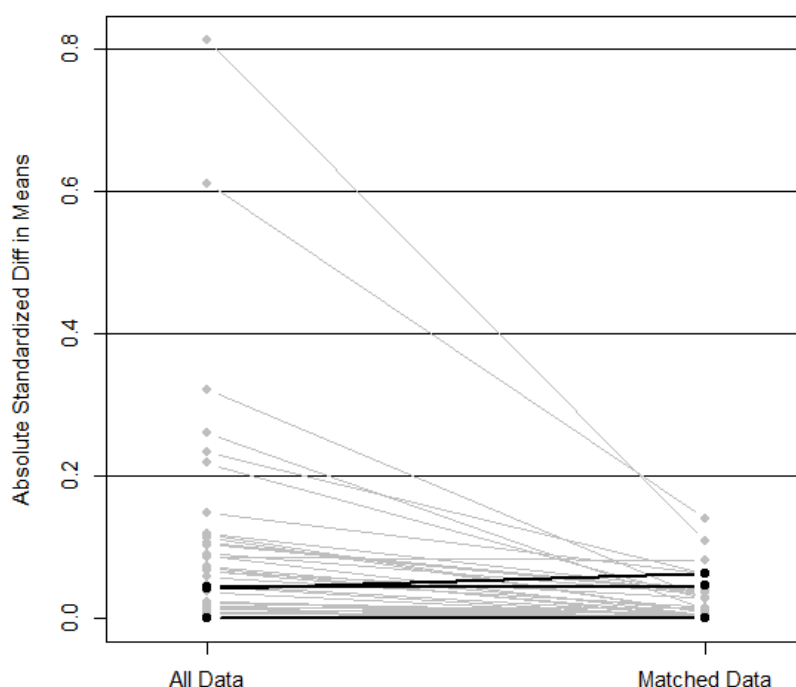
Matched Control Units -> Matched control units

Unmatched Control Units -> Unmatched control units

Propensity Score -> Propensity score

Figure 3

Trend in standardized differences of baseline characteristics before and after propensity score matching.



Correcciones a la figura

Absolute Standardized Diff in Means -> Absolute standardized mean differences

All Data -> All data

Matched Data -> Matched data

Survival-time inverse probability weighting propensity score analysis

Survival-time inverse probability weighting propensity score analysis (IPW) was used to evaluate the association between ACEI/ARB use and mortality. IPW uses weights based on the propensity score to create a synthetic sample in which the distribution of measured baseline covariates is independent of treatment assignment. Estimated treatment effects are not confounded in the sample weighted using the IPW, if all confounding baseline covariates are considered. Furthermore, in the weighted sample, the distribution of baseline covariates in each treatment group will be the same as the distribution of baseline covariates in the overall unweighted sample. Survival-time IPW regression adjustment use

missingness-adjusted regression coefficients to compute averages of treatment level predicted outcomes. Contrasts of these averages estimate the treatment effects.

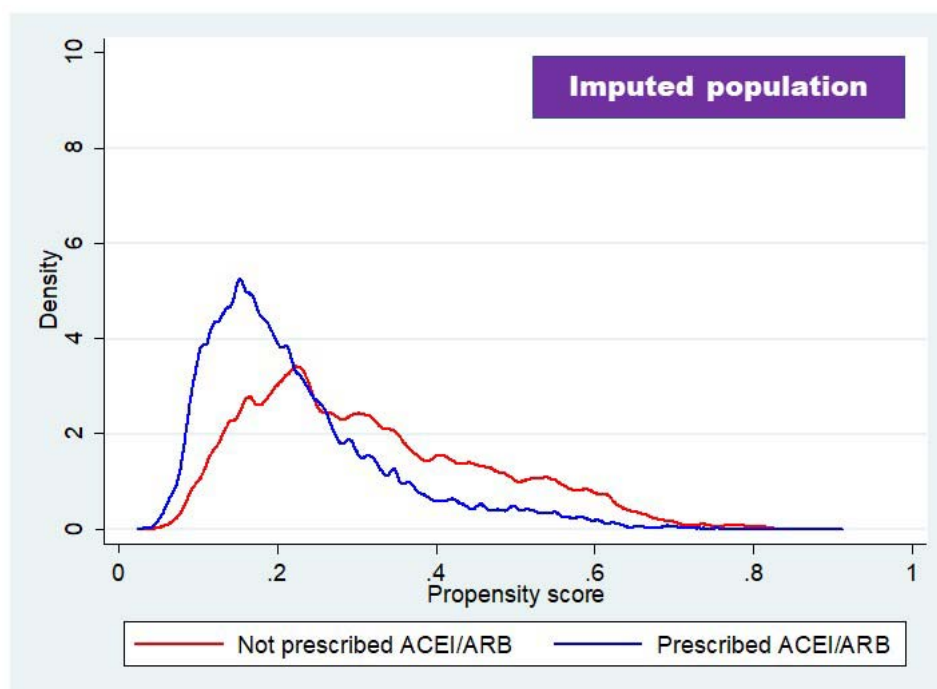
Augmented inverse probability weights (AIPW)

When analyzing data with missing values, a commonly used method is the IPW method, which reweights estimating equations with propensity scores. The popularity of the IPW method is due to its simplicity. However, it is often criticized for being inefficient because most of the information from the incomplete observations is not used. An alternative estimator is the AIPW estimator, which combines both the properties of the regression-based estimator and the IPW estimator. It is therefore a “doubly robust” method in that it only requires either the propensity or outcome model to be correctly specified but not both. This method augments the IPW estimator to reduce variability and improve estimate efficiency, and with the double-robust property, it yields unbiased estimates if either the mortality regression or propensity scores are properly specified. We used the AIPW to calculate the average treatment effects (ATE). For each patient, the effect of treatment is defined as $Y_{i(1)} - Y_{i(0)}$: the difference between the 2 potential outcomes. The ATE is $E[Y_{i(1)} - Y_{i(0)}]$, the average effect of moving an entire population from untreated to treated. In our study, the ATE coefficient assesses the impact of ACEI/ARB in reducing the death rate, evaluating the absolute risk difference. Therefore, for example, a significant negative ATE risk difference of 0.05 would indicate that the 1-year death rate in a patient treated with ACEI/ARB would be 5% lower than in an untreated patient. One of the assumptions required to use the ATE is the overlap assumption, which states that each individual has a positive probability of receiving each treatment level. If the effects overlap, a postestimation STATA command plots the estimated densities of the probability of getting each treatment level. These plots were used to check whether the overlap assumption is violated. The results of the assessment of the overlap assumption are shown in the next pages. The minimum propensity score for each treatment level was

sufficiently greater than zero and the maximum propensity score for each treatment level sufficiently less than 1, thus the assumption was not violated.

Figure 4

Overlap assumption assessment plots for imputed population.



ACEI/ARB, angiotensin converting-enzyme inhibitors/angiotensin receptor blockers.

Neither plot indicates too much probability mass near 0 or 1, and the 2 estimated densities have most of their respective masses in regions in which they overlap. Thus there is no evidence that the overlap assumption is violated.

INSTRUMENTAL VARIABLE ANALYSIS

To mitigate potential selection bias introduced by measured or unmeasured confounding in observational data, an instrumental variable analysis was performed. The use of instrumental variable analysis allowed us to determine the association between the use of ACEI/ARB and survival, while using an instrument to behave like a natural randomization of patients to hospitals that differ in their likelihood of receiving treatment, and to provide closer approximations to the average population effects from randomized clinical trials.

We used annual hospital rates of prescription of guideline-indicated treatments (DAPT, beta-blockers, statins and ACEI/ARB) as the instrumental variable. Our choice was informed by clinical knowledge and past literature that has found that “physician prescribing preference” is a good instrument for investigating drug effectiveness when using instrumental variable. We hypothesized that hospital prescribing rates of discharge medications as an instrument would behave similarly to physician prescribing preferences. The validity of the instrument was confirmed by checking that it was correlated with receipt of ACEI/ARB at discharge, was independent of other patient characteristics, and was independent of patient outcomes. To test the first assumption we used a logistic regression model to predict ACEI/ARB use at discharge as a function of hospital prescribing rates, for assumption 2 we compared patient characteristics across quintiles of the instrument, and for the third assumption we regressed mortality on the instrumental variable after adjusting for ACEI/ARB use at discharge and other patient characteristics (Table 3). We found that the instrument variable was a good predictor of beta-blocker use (OR, 1.03, 95% CI, 1.02-1.04; $P < .001$), was quite well balanced across patient characteristics (Table 3) and was independent of the patient outcomes (1-year mortality; OR, 1.00, 95% CI, 0.99 to 1.01, $P = .567$) to therefore meet the required assumptions as a valid instrument.

In our study, the coefficient of instrumental variable analysis assesses the effect of ACEI/ARB on survival in relative terms. Therefore, for example, a significant negative coefficient of 0.5 would indicate that the 1-year death rate in a patient treated with ACEI/ARB would be 50% less than in an untreated patient.

Table 3

Patient characteristics and mortality according to quintiles of hospital prescribing rates of the 4 treatments (dual antiplatelet therapy, beta-blockers, statins, and angiotensin converting-enzyme inhibitors/angiotensin receptor blockers) at discharge

| | Quintile of hospital prescribing rates of the 4 treatments at discharge | | | | |
|--|---|---------------|---------------|---------------|---------------|
| Variable | 1 n = 3089 | 2 n = 3254 | 3 n = 3451 | 4 n = 2983 | 5 n = 2624 |
| Age, y | 63.4 ± 12.6 | 63.2 ± 12.3 | 62.5 ± 12.6 | 65.1 ± 12.9 | 64.2 ± 12.9 |
| Female sex | 844 (27.3) | 768 (23.6) | 769 (22.3) | 661 (22.1) | 550 (21.0) |
| Diabetes mellitus | 677 (21.9) | 726 (22.3) | 871 (25.2) | 778 (26.1) | 647 (24.6) |
| Hypertension | 1604 (51.9) | 1877 (57.7) | 2087 (60.5) | 1837 (61.6) | 1631 (62.1) |
| Dyslipidemia | 1094 (35.4) | 1934 (59.4) | 2136 (61.9) | 1557 (52.2) | 1370 (52.2) |
| Peripheral artery disease | 151 (4.9) | 186 (5.7) | 203 (5.9) | 217 (7.3) | 149 (5.7) |
| Prior myocardial infarction | 375 (12.1) | 348 (10.7) | 400 (11.6) | 388 (13.0) | 331 (12.6) |
| Prior heart failure | 90 (2.9) | 149 (4.6) | 93 (2.7) | 73 (2.4) | 103 (3.9) |
| Unstable angina | 582 (18.8) | 379 (11.6) | 382 (11.1) | 398 (13.3) | 317 (12.1) |
| ST-segment elevation myocardial infarction | 2280 (73.8) | 1553 (47.7) | 2145 (62.2) | 1508 (50.6) | 1451 (55.3) |
| Killip ≥ II | 400 (12.9) | 424 (13.0) | 532 (15.4) | 392 | 325 (12.4) |
| Left ventricular ejection fraction | 55.1 ± 8.7 | 50.6 ± 10.9 | 51.9 ± 10.6 | 54.7 ± 11.3 | 51.2 ± 10.8 |
| Hemoglobin at admission, g/dL | 13.9 ± 1.9 | 14.3 ± 1.7 | 14.1 ± 1.8 | 13.9 ± 1.7 | 13.8 ± 1.8 |
| Creatinine at admission, mg/dL | 0.9 ± 0.5 | 0.9 ± 0.4 | 0.9 ± 0.5 | 1.0 ± 0.5 | 1.0 ± 0.5 |
| Multivessel coronary disease | 1278 (41.4) | 1574 (48.4) | 1707 (49.4) | 1554 (52.1) | 1403 (53.5) |
| Complete revascularization | 2017 (65.3) | 1939 (59.6) | 1939 (56.2) | 1788 (59.9) | 1736 (66.2) |

Data are expressed as mean \pm standard deviation or No. (%).

MULTIPLE IMPUTATION

MULTIPLE IMPUTATIONS

For multiple imputations, we used as multiple imputation algorithm the fully conditional specification, also termed “chained equations” [SPSS Inc: Build Better Models When You Fill in the Blanks. 2014]. This is a more flexible approach to imputation in that it is designed to handle different types of variables (continuous, binary, categorical, ordinal) and does not assume multivariate normality of the data. In practice, fully conditional specification involves running a series of regression models such that each variable with missing data is regressed on the other variables in the data set according to its distribution. So, for example, categorical variables will be modelled using logistic regression and continuous variables will be modelled using linear regression. Imputation by fully conditional specification, as applied in SPSS, is also an iterative process that starts by imputing every missing value with random draws from the distribution of the nonmissing values. Continuous variables are replaced with draws from a normal distribution and categorical variables are replaced with draws from a multinomial distribution.

Each iteration involves the following steps:

1. Set the “place holders” of 1 variable that has missing values back to missing.
2. Set up a regression equation, according to the distribution of the variable, with the observed values as the dependent variable and the other variables as independent variables.
3. Replace the missing values from this variable with predictions from the regression equation.
4. Repeat these steps for each variable that has missing values.

This forms 1 iteration of the process. At each iteration the imputed values are updated. This process is repeated for a specified number of iterations, n , after which the data set is retained as 1 complete imputed data set. The number of iterations, n , chosen so that the parameters from the regression models have stabilized, is generally about 10. This entire process is repeated until the required number, m , of imputed data sets is generated. With regard to the number of imputations that should be performed, it has recently been suggested to apply a reasonable number of imputations (> 5) to avoid producing a large Monte Carlo error. On the basis of the percentage of data missing in this study (4.0%;

23 097 data from a total of 546 740 data), and taking account the recommendations for the number of imputations as a function of the fraction of missing information, 10 sets of data were imputed. Although, in the past, it was widely thought that as few as 3 imputed data sets are needed to obtain good results and inferences, new studies have shown that this may, in fact, not be enough. Studies have shown that there could be an important reduction in statistical power if m is small.

Each of the m data sets were analyzed with Cox regression—the chosen method of analysis—and the results were combined using Rubin's rules. For the PS matching after multiple imputation, we averaged the m propensity scores for each record across the completed datasets, and performed PS matching with these averaged scores to estimate the treatment effect. We also estimated the impact of ACEI/ARB using PS matching within each completed data set.

IMPUTED DATASETS ANALYSIS

Repeating the analysis of the study in each imputed dataset

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 1

| Dataset 1 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.620 | 0.522-0.737 | < .001 |
| | Multivariate | 0.768 | 0.640-0.923 | .005 |
| | Adjusted by IPW | 0.767 | 0.638-0.922 | .005 |
| | After PS matching | 0.722 | 0.576-0.905 | .005 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | 0.015 to -0.001 | .034 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.232 | -0.326 to -0.138 | < .001 |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.389 | 0.284-0.533 | < .001 |
| | Multivariate | 0.596 | 0.419-0.848 | .004 |
| | Adjusted by IPW | 0.528 | 0.371-0.752 | < .001 |
| | After PS matching | 0.528 | 0.345-0.809 | .003 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.027 | -0.055 to 0.002 | .066 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.470 | -0.668 to -0.273 | < .001 |
| LVEF > 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.696 | 0.565-0.856 | .001 |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Multivariate | 0.826 | 0.664-1.028 | .087 |
| | Adjusted by IPW | 0.884 | 0.710-1.100 | .268 |
| | After PS matching | 0.826 | 0.637-1.070 | .148 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.005 | -0.012 to 0.002 | .152 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.145 | -0.252 to -0.037 | .008 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Multivariate adjustment was conducted for age, female sex, country, year, diabetes mellitus, hypertension, dyslipidemia, peripheral artery disease, prior myocardial infarction, prior heart failure, prior stroke, known malignant disease, unstable angina, ST-segment elevation myocardial infarction, Killip \geq II, left ventricular ejection fraction, hemoglobin at admission, creatinine at admission, multivessel coronary disease, complete revascularization, dual antiplatelet therapy, oral anticoagulation, beta-blockers, and statins.

Table 5

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 2

| Dataset 2 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.619 | 0.520-0.735 | < .001 |
| | Multivariate | 0.766 | 0.638-0.921 | .004 |
| | Adjusted by IPW | 0.763 | 0.635-0.916 | .004 |
| | After PS matching | 0.753 | 0.604-0.937 | .011 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | -0.015 to -0.001 | .034 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.233 | -0.327 to -0.139 | <.001 |
| | | | | |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.413 | 0.299-0.572 | < .001 |
| | Multivariate | 0.647 | 0.450-0.932 | .019 |
| | Adjusted by IPW | 0.558 | 0.389-0.802 | .002 |
| | After PS matching | 0.565 | 0.365-0.873 | .010 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.029 | -0.059 to 0.001 | .056 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.437 | -0.639 to -0.236 | < .001 |
| | | | | |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.669 | 0.545-0.821 | < .001 |
| | Multivariate | 0.803 | 0.648-0.994 | .044 |
| | Adjusted by IPW | 0.850 | 0.686-1.055 | .140 |
| | After PS matching | 0.842 | 0.656-1.080 | .176 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.006 | -0.013 to 0.001 | .111 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.162 | -0.269 to -0.055 | .003 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval;

HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS,

propensity score.

Table 6

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 3

| Dataset 3 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.613 | 0.516-0.728 | < .001 |
| | Multivariate | 0.750 | 0.624-0.901 | .002 |
| | Adjusted by IPW | 0.755 | 0.629-0.907 | .003 |
| | After PS matching | 0.705 | 0.567-0.877 | .003 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.009 | -0.016 to -0.001 | .021 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.236 | -0.329 to -0.142 | < .001 |
| | | | | |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.397 | 0.288-0.547 | < .001 |
| | Multivariate | 0.634 | 0.442-0.910 | .014 |
| | Adjusted by IPW | 0.518 | 0.363-0.741 | < .001 |
| | After PS matching | 0.437 | 0.279-0.685 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.024 | -0.050 to 0.028 | .079 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.479 | -0.680 to -0.278 | <0.001 |
| | | | | |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.672 | 0.547-0.824 | < .001 |
| | Multivariate | 0.789 | 0.636-0.979 | .031 |
| | Adjusted by IPW | 0.859 | 0.692-1.066 | .168 |
| | After PS matching | 0.817 | 0.635-1.052 | .117 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.006 | -0.013 to 0.001 | .084 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.153 | -0.260 to -0.045 | .005 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 7

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 4

| Dataset 4 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox Regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.613 | 0.516-0.729 | < .001 |
| | Multivariate | 0.758 | 0.631-0.911 | .003 |
| | Adjusted by IPW | 0.755 | 0.628-0.907 | .003 |
| | After PS matching | 0.712 | 0.571-0.888 | .003 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | -0.016 to -0.001 | .031 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.236 | -0.330 to -0.143 | < .001 |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.406 | 0.293-0.562 | < .001 |
| | Multivariate | 0.625 | 0.433-0.901 | .012 |
| | Adjusted by IPW | 0.536 | 0.372-0.771 | .001 |
| | After PS matching | 0.370 | 0.224-0.613 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.022 | -0.050 to 0.006 | .123 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.443 | -0.646 to -0.239 | < .001 |
| LVEF > 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.664 | 0.542-0.815 | < .001 |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Multivariate | 0.796 | 0.642 | .986 |
| | Adjusted by IPW | 0.849 | 0.685-1.053 | .137 |
| | After PS matching | 0.849 | 0.662-1.090 | .199 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.006 | -0.014 to 0.001 | .080 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.164 | -0.271 to -0.058 | .002 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 8

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 5

| Dataset 5 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.609 | 0.513-0.724 | <.001 |
| | Multivariate | 0.762 | 0.634-0.915 | .004 |
| | Adjusted by IPW | 0.753 | 0.627-0.904 | .002 |
| | After PS matching | 0.703 | 0.565-0.875 | .002 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | -0.016 to -0.001 | .029 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.242 | -0.336 to -0.149 | < .001 |
| | | | | |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.387 | 0.282-0.532 | < .001 |
| | Multivariate | 0.626 | 0.439-0.893 | .010 |
| | Adjusted by IPW | 0.513 | 0.361-0.730 | < .001 |
| | After PS matching | 0.382 | 0.237-0.614 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.025 | -0.055 to 0.005 | .112 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.467 | -0.667 to -0.266 | < .001 |
| | | | | |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.671 | 0.546-0.824 | < .001 |
| | Multivariate | 0.808 | 0.650-1.003 | .053 |
| | Adjusted by IPW | 0.862 | 0.693-1.071 | .179 |
| | After PS matching | 0.839 | 0.654-1.078 | .169 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.006 | -0.013 to 0.001 | .106 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.163 | -0.270 to -0.050 | .003 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 9

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 6

| Dataset 6 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox Regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.613 | 0.516-0.728 | < .001 |
| | Multivariate | 0.759 | 0.632-0.911 | .003 |
| | Adjusted by IPW | 0.757 | 0.630-0.909 | .003 |
| | After PS matching | 0.696 | 0.559-0.867 | .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | -0.015 to -0.001 | .032 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.237 | -0.330 to -0.143 | < .001 |
| | | | | |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.414 | 0.301-0.570 | < .001 |
| | Multivariate | 0.641 | 0.448-0.917 | .015 |
| | Adjusted by IPW | 0.582 | 0.405-0.837 | .003 |
| | After PS matching | 0.376 | 0.234-0.605 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.026 | -0.055 to 0.002 | .067 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.453 | -0.656 to -0.244 | < .001 |
| | | | | |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.664 | 0.541-0.815 | < .001 |
| | Multivariate | 0.801 | 0.645-0.994 | .044 |
| | Adjusted by IPW | 0.839 | 0.676-1.042 | .112 |
| | After PS matching | 0.834 | 0.649-1.072 | .156 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.005 | -0.013 to 0.001 | .101 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.164 | -0.271 to -0.056 | .003 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 10

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 7

| Dataset 7 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.613 | 0.516-0.729 | < .001 |
| | Multivariate | 0.749 | 0.624-0.899 | .002 |
| | Adjusted by IPW | 0.753 | 0.627-0.905 | .002 |
| | After PS matching | 0.688 | 0.552-0.859 | .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.008 | -0.016 to -0.001 | .029 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.233 | -0.327 to -0.140 | < .001 |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.368 | 0.269-0.503 | < .001 |
| | Multivariate | | | |
| | Adjusted by IPW | 0.500 | 0.351-0.712 | < .001 |
| | After PS matching | 0.353 | 0.220-0.568 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.033 | -0.062 to -0.002 | .032 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.486 | -0.684 to -0.287 | < .001 |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.691 | 0.562-0.851 | < .001 |
| | Multivariate | 0.819 | 0.658-1.019 | .073 |
| | Adjusted by IPW | 0.875 | 0.703-1.088 | .230 |
| | After PS matching | 0.833 | 0.646-1.074 | .158 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.005 | -0.012 to 0.002 | .137 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.144 | -0.252 to -0.037 | .009 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 11

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 8

| Dataset 8 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.618 | 0.520-0.734 | < .001 |
| | Multivariate | 0.762 | 0.634-0.916 | .004 |
| | Adjusted by IPW | 0.764 | 0.636-0.918 | .004 |
| | After PS matching | 0.685 | 0.549-0.855 | .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | −0.008 | −0.015 to −0.001 | .034 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | −0.234 | −0.328 to −0.140 | <.001 |
| | | | | |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.395 | 0.286-0.544 | < .001 |
| | Multivariate | | | |
| | Adjusted by IPW | 0.517 | 0.360-0.742 | < .001 |
| | After PS matching | 0.362 | 0.222-0.592 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | −0.028 | −0.056 to 0.001 | .055 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | −0.467 | −0.668 to −0.266 | < .001 |
| | | | | |
| EF ^ | Cox regression | HR | 95% CI | <i>P</i> |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.689 | 0.561-0.846 | < .001 |
| | Multivariate | 0.822 | 0.662-1.020 | .075 |
| | Adjusted by IPW | 0.881 | 0.710-1.094 | .252 |
| | After PS matching | 0.825 | 0.640-1.061 | .134 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.005 | -0.012 to 0.002 | .162 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.152 | -0.259 to -0.045 | .005 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 12

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 9

| Dataset 9 | | | | |
|-----------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.624 | 0.525-0.742 | < .001 |
| | Multivariate | 0.779 | 0.648-0.937 | .008 |
| | Adjusted by IPW | 0.776 | 0.646-0.933 | .007 |
| | After PS matching | 0.709 | 0.570-0.882 | .002 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.007 | -0.015 to 0.001 | .051 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.234 | -0.327 to -0.140 | < .001 |
| | Cox regression | HR | 95% CI | <i>P</i> |
| LVEF ≤ 40 | Univariate | 0.380 | 0.273-0.528 | < .001 |
| | Multivariate | 0.627 | 0.435-0.905 | .013 |
| | Adjusted by IPW | 0.499 | 0.347-0.718 | < .001 |
| | After PS matching | 0.371 | 0.231-0.597 | < .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.026 | -0.053 to 0.001 | .061 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.482 | -0.689 to -0.274 | < .001 |
| | Cox regression | HR | 95% CI | <i>P</i> |
| | | | | |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Univariate | 0.679 | 0.554-0.832 | < .001 |
| | Multivariate | 0.827 | 0.667-1.025 | .083 |
| | Adjusted by IPW | 0.876 | 0.707-1.087 | .230 |
| | After PS matching | 0.830 | 0.648-1.064 | .141 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.005 | -0.012 to 0.002 | .166 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.161 | -0.267 to -0.054 | .003 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Table 13

Analysis of prognostic impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in Dataset 10

| Dataset 10 | | | | |
|------------|-----------------------|-------------|------------------|----------|
| Total | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.625 | 0.526-0.743 | < .001 |
| | Multivariate | 0.768 | 0.639-0.923 | .005 |
| | Adjusted by IPW | 0.770 | 0.641-0.925 | .005 |
| | After PS matching | 0.754 | 0.607-0.937 | .011 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | −0.007 | −0.015 to −0.001 | .047 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | −0.228 | −0.321 to −0.054 | .003 |
| LVEF ≤ 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.428 | 0.309-0.593 | < .001 |
| | Multivariate | 0.646 | 0.449-0.930 | .019 |
| | Adjusted by IPW | 0.574 | 0.400-0.825 | .003 |
| | After PS matching | 0.427 | 0.262-0.697 | .001 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | −0.023 | −0.051 to 0.006 | .117 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | −0.432 | −0.637 to −0.226 | < .001 |
| LVEF > 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | Univariate | 0.671 | 0.547-0.823 | < .001 |

| | | | | |
|--|-----------------------|-------------|------------------|----------|
| | Multivariate | 0.804 | 0.647-0.997 | .047 |
| | Adjusted by IPW | 0.856 | 0.690-1.062 | .157 |
| | After PS matching | 0.882 | 0.690-1.128 | .318 |
| | AIPW | ATE | 95% CI | <i>P</i> |
| | | -0.006 | -0.013 to 0.001 | .109 |
| | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | -0.161 | -0.268 to -0.055 | .003 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

COMPLETE CASE ANALYSIS

Repeating the analysis of the study after excluding those cases with missing values

Table 14

Baseline characteristics in case-complete population showing missing values

| ACEI/ARB at hospital discharge* | | | | |
|---------------------------------|----------------------------|-------------------------|--------|--------------|
| Variables | Yes (n = 11 433; 74.2%) | No (n = 3777; 24.5%) | P | Missing |
| Age, y | 63.7 ± 12.6 | 63.5 ± 13.0 | .406 | 0 |
| Female sex, % | 22.5 | 25.4 | < .001 | 0 |
| Region, % | | | | |
| Europe | 67.1 | 60.0 | < .001 | 0 |
| America | 18.5 | 21.9 | | |
| Asia | 14.4 | 18.1 | | |
| Year, | | | | |
| 2003-2006 | 20.2 | 30.3 | < .001 | 0 |
| 2007-2010 | 45.2 | 47.6 | | |
| 2011-2015 | 34.6 | 22.1 | | |
| Diabetes mellitus, % | 24.7 | 21.5 | < .001 | 0 |
| Hypertension, % | 61.3 | 50.5 | < .001 | 0 |
| Dyslipidemia, % | 53.6 | 49.1 | < .001 | 123 (0.8%) |
| Peripheral artery disease, % | 5.8 | 5.9 | .889 | 0 |
| Prior myocardial infarction, % | 12.0 | 11.6 | .554 | 0 |
| Prior heart failure, % | 3.3 | 3.3 | .941 | 1774 (11.5%) |
| Prior stroke, % | 5.8 | 6.3 | .239 | 0 |

| | | | | |
|--|----------------|----------------|--------|--------------|
| Known malignant disease, % | 5.6 | 7.0 | .003 | 0 |
| Unstable angina, % | 12.9 | 14.5 | .013 | 0 |
| ST-segment elevation myocardial infarction, % | 58.7 | 56.6 | .020 | 0 |
| Killip \geq II | 14.2 | 12.3 | .012 | 3324 (21.6%) |
| Left ventricular ejection fraction \leq 40%, % | 16.7 | 13.3 | < .001 | 5305 (34.4%) |
| Hemoglobin at admission, g/dL | 14.0 \pm 1.8 | 13.8 \pm 1.8 | < .001 | 1297 (8.4%) |
| Creatinine at admission, mg/dL | 0.9 \pm 0.4 | 1.0 \pm 0.7 | < .001 | 570 (3.7%) |
| Multivessel coronary disease, % | 48.6 | 47.5 | .334 | 4380 (28.4%) |
| Drug-eluting stent, % | 39.9 | 37.9 | .027 | 0 |
| Complete revascularization, % | 61.2 | 56.1 | < .001 | 3674 (23.9%) |
| Dual Antiplatelet Therapy, % | 94.9 | 93.0 | < .001 | 0 |
| Oral anticoagulation, % | 5.4 | 3.9 | < .001 | 0 |
| Beta-blockers, % | 86.0 | 64.6 | < .001 | 191 (1.2%) |
| Statins, % | 94.3 | 88.8 | < .001 | 123 (0.8%) |
| In-hospital reinfarction, % | 1.3 | 1.4 | .759 | 125 (0.8) |
| In-hospital heart failure, % | 4.4 | 4.2 | .572 | 1897 (12.3) |

ACEI/ARB, angiotensin converting-enzyme inhibitors/angiotensin receptor blockers.

Unless otherwise indicated, data are expressed as mean \pm standard deviation.

* Missing values for ACEI/ARB therapy at hospital discharge = 191 (1.2%).

Table 15

Detailed balance of propensity score matching

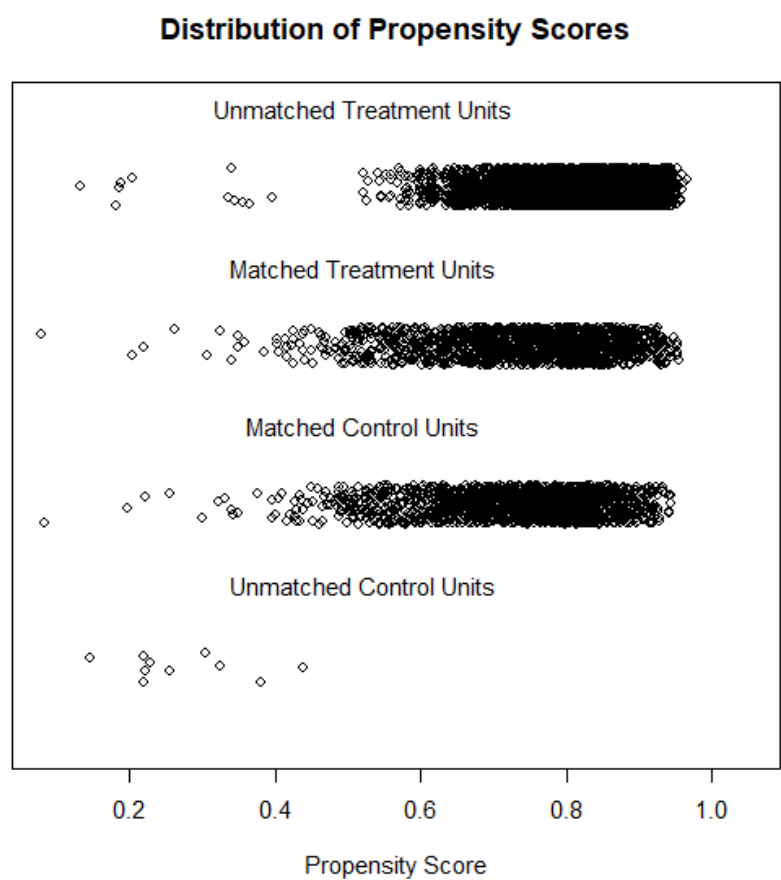
| Subsamples | Covariates | Means treated | | Means control | | SD control | | Std. mean diff. | |
|-------------|-----------------------------|---------------|----------|---------------|----------|------------|--------|-----------------|--------|
| | | Before | After | Before | After | Before | After | Before | After |
| (all cases) | propensity | 0.800 | 0.744 | 0.730 | 0.733 | 0.123 | 0.117 | 0.691 | 0.104 |
| | Age | 63.946 | 63.648 | 63.918 | 63.858 | 13.488 | 13.473 | 0.002 | -0.017 |
| | Female | 0.216 | 0.230 | 0.234 | 0.232 | 0.423 | 0.422 | -0.042 | -0.005 |
| | Year | 2009.29 | 2008.738 | 2008.691 | 2008.698 | 2.737 | 2.738 | 0.231 | 0.015 |
| | | 1 | | | | | | | |
| | Country | 0.172 | 0.240 | 0.237 | 0.236 | 0.425 | 0.425 | -0.172 | 0.012 |
| | Diabetes | 0.270 | 0.263 | 0.253 | 0.253 | 0.435 | 0.435 | 0.039 | 0.022 |
| | Hypertension | 0.626 | 0.524 | 0.485 | 0.484 | 0.500 | 0.500 | 0.291 | 0.082 |
| | Dyslipidemia | 0.506 | 0.493 | 0.489 | 0.491 | 0.500 | 0.500 | 0.034 | 0.004 |
| | Peripheral artery disease | 0.072 | 0.065 | 0.078 | 0.078 | 0.268 | 0.268 | 0.022 | -0.049 |
| | Prior myocardial infarction | 0.123 | 0.113 | 0.116 | 0.116 | 0.320 | 0.320 | 0.022 | -0.008 |
| | Prior Heart Failure | 0.027 | 0.028 | 0.030 | 0.030 | 0.170 | 0.170 | -0.016 | -0.012 |
| | Prior Stroke | 0.060 | 0.072 | 0.063 | 0.063 | 0.244 | 0.243 | -0.012 | 0.039 |
| | History of Cancer | 0.053 | 0.067 | 0.071 | 0.069 | 0.256 | 0.254 | -0.079 | -0.009 |
| | Unstable Angina | 0.112 | 0.147 | 0.158 | 0.155 | 0.365 | 0.362 | -0.147 | -0.027 |

| | | | | | | | | |
|--|--------|--------|--------|--------|--------|--------|--------|--------|
| ST-segment elevation myocardial infarction | 0.576 | 0.560 | 0.547 | 0.550 | 0.498 | 0.498 | 0.058 | 0.020 |
| Killip > 1 | 0.158 | 0.155 | 0.157 | 0.157 | 0.364 | 0.364 | 0.003 | -0.004 |
| Left Ventricular Ejection Fraction | 53.013 | 54.710 | 54.925 | 54.897 | 10.783 | 10.766 | -0.175 | -0.017 |
| Creatinine | 0.937 | 0.968 | 1.043 | 1.017 | 0.65 | 0.657 | -0.242 | -0.112 |
| Hemoglobine | 14.078 | 13.794 | 13.735 | 13.756 | 1.829 | 1.811 | 0.198 | 0.022 |
| Multivessel | 0.505 | 0.498 | 0.505 | 0.505 | 0.500 | 0.500 | -0.001 | -0.013 |
| Drug-Eluting Stent | 0.469 | 0.542 | 0.533 | 0.534 | 0.499 | 0.499 | -0.128 | 0.017 |
| Complete revascularization | 0.634 | 0.566 | 0.572 | 0.572 | 0.495 | 0.495 | 0.129 | -0.012 |
| Dual Antiplatelet Therapy | 0.973 | 0.965 | 0.959 | 0.959 | 0.198 | 0.197 | 0.085 | 0.037 |
| Oral anticoagulation | 0.057 | 0.044 | 0.041 | 0.041 | 0.198 | 0.197 | 0.069 | 0.014 |
| Beta-blockers | 0.841 | 0.749 | 0.740 | 0.741 | 0.439 | 0.438 | 0.277 | 0.022 |
| Statins | 0.930 | 0.898 | 0.896 | 0.898 | 0.305 | 0.303 | 0.130 | 0.000 |
| In-hospital Reinfarction | 0.018 | 0.025 | 0.026 | 0.026 | 0.158 | 0.159 | -0.055 | -0.005 |
| In-hospital Heart Failure | 0.058 | 0.057 | 0.060 | 0.060 | 0.238 | 0.238 | -0.008 | -0.014 |

SD, standard deviation; Std. mean diff., standardized mean differences.

Figure 5

Distribution of propensity scores.



Correcciones a la figura

Propensity Score → Propensity score

Unmatched Treatment Units → Unmatched treatment units

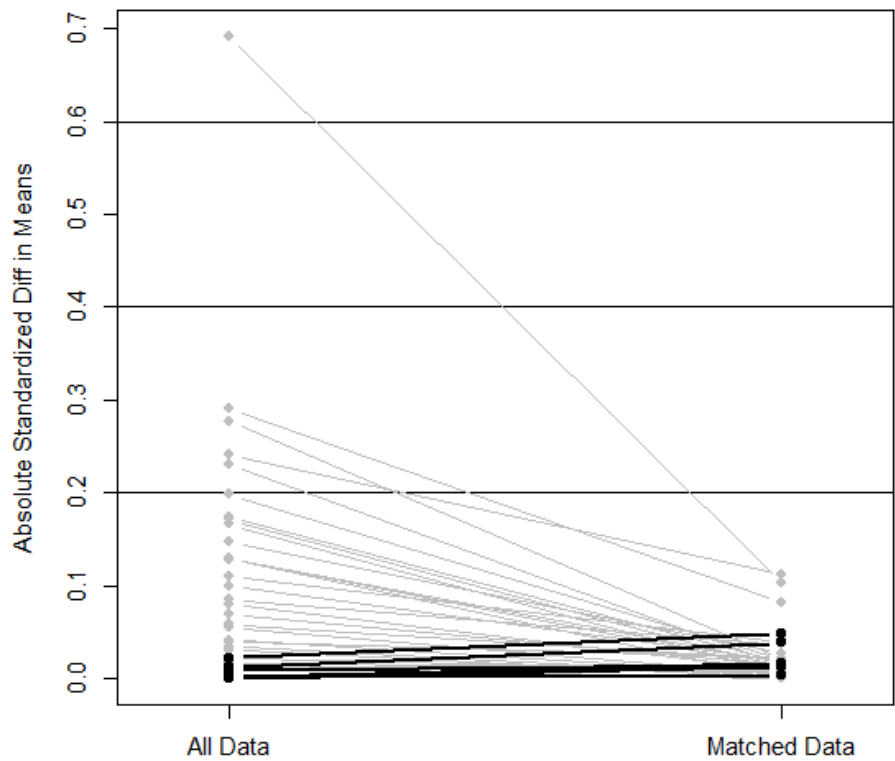
Matched Treatment Units → Matched treatment units

Matched Control Units → Matched control units

Unmatched Control Units → Unmatched control units

Figure 6

Trend in standardized differences of baseline characteristics before and after propensity score matching.



Correcciones a la figura

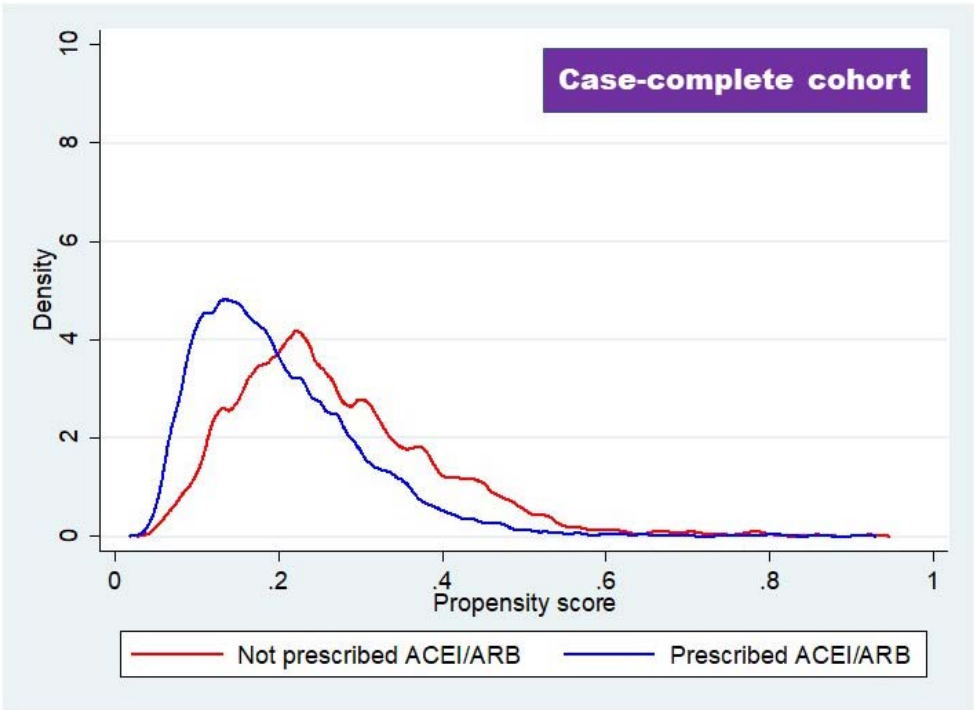
Absolute Standardized Diff in Means → Absolute standardized mean differences

All Data → All data

Matched Data → Matched data

Figure 7

Overlap assumption assessment plots for imputed population.



Neither plot indicates too much probability mass near 0 or 1, and the 2 estimated densities have most of their respective masses in regions in which they overlap each other. Thus there is no evidence that the overlap assumption is violated.

ACEI/ARB, angiotensin converting-enzyme inhibitors/angiotensin receptor blockers.

Table 16

Different analysis to assess the prognostic role of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers in 1-year mortality

| Population | | Analysis | Complete cases | | |
|-----------------------------------|--|-------------------------|----------------|------------------|----------|
| Total population | | Cox regression | HR | 95% CI | <i>P</i> |
| | | Univariate | 0.582 | 0.453-0.749 | < .001 |
| | | Multivariate* | 0.716 | 0.550-0.933 | .013 |
| | | Adjusted by IPW | 0.650 | 0.500-0.845 | .001 |
| | | After PS matching | 0.616 | 0.438-0.868 | .006 |
| | | AIPW | Coefficient | 95% CI | <i>P</i> |
| | | ATE (risk difference) | -0.010 | -0.021 to 0.002 | .094 |
| | | Instrumental Variable | Coefficient | 95% CI | <i>P</i> |
| | | Relative risk reduction | -0.295 | -0.440 to -0.150 | < .001 |
| | | | | | |
| Subgroups by LVEF LVEF ≤ 40 | | Cox Regression | HR | 95% CI | HR |
| | | Univariate | 0.407 | 0.272-0.610 | < .001 |
| | | Multivariate* | 0.670 | 0.428-1.049 | .080 |

| | | | | | |
|--|-----------|-------------------------|-------------|------------------|----------|
| | | Adjusted by IPW | 0.487 | 0.317-0.746 | .001 |
| | | After PS matching | 0.427 | 0.229-0.798 | .008 |
| | | AIPW | Coefficient | 95% CI | <i>P</i> |
| | | ATE (risk difference) | -0.025 | -0.063 to 0.013 | .197 |
| | | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | Relative risk reduction | -0.452 | -0.728 to -0.174 | .001 |
| | LVEF > 40 | Cox regression | HR | 95% CI | <i>P</i> |
| | | Univariate | 0.638 | 0.463-0.879 | .006 |
| | | Multivariate* | 0.720 | 0.513-1.009 | .057 |
| | | Adjusted by IPW | 0.741 | 0.531-1.034 | .078 |
| | | After PS matching | 0.744 | 0.494-1.120 | .156 |
| | | AIPW | Coefficient | 95% CI | <i>P</i> |
| | | ATE (risk difference) | -0.009 | -0.020 to 0.019 | .107 |
| | | Instrumental variable | Coefficient | 95% CI | <i>P</i> |
| | | Relative risk reduction | -0.209 | -0.384 to -0.034 | .019 |

AIPW, augmented inverse probability weighting; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; IPW, inverse probability weighting; LVEF, left ventricular ejection fraction; PS, propensity score.

Multivariate adjustment for age, female sex, country, year, diabetes mellitus, hypertension, dyslipemia, peripheral artery disease, prior myocardial infarction, prior heart failure, prior stroke, known malignant disease, unstable angina, ST-segment elevation myocardial infarction, Killip \geq II, left ventricular ejection fraction, hemoglobin at admission, creatinine at admission, multivessel coronary disease, complete revascularization, dual antiplatelet therapy, oral anticoagulation, beta-blockers, and statins.

Figure 8

Impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) on 1-year mortality according to left ventricular ejection fraction (LVEF) as continuous variable (unadjusted analysis).

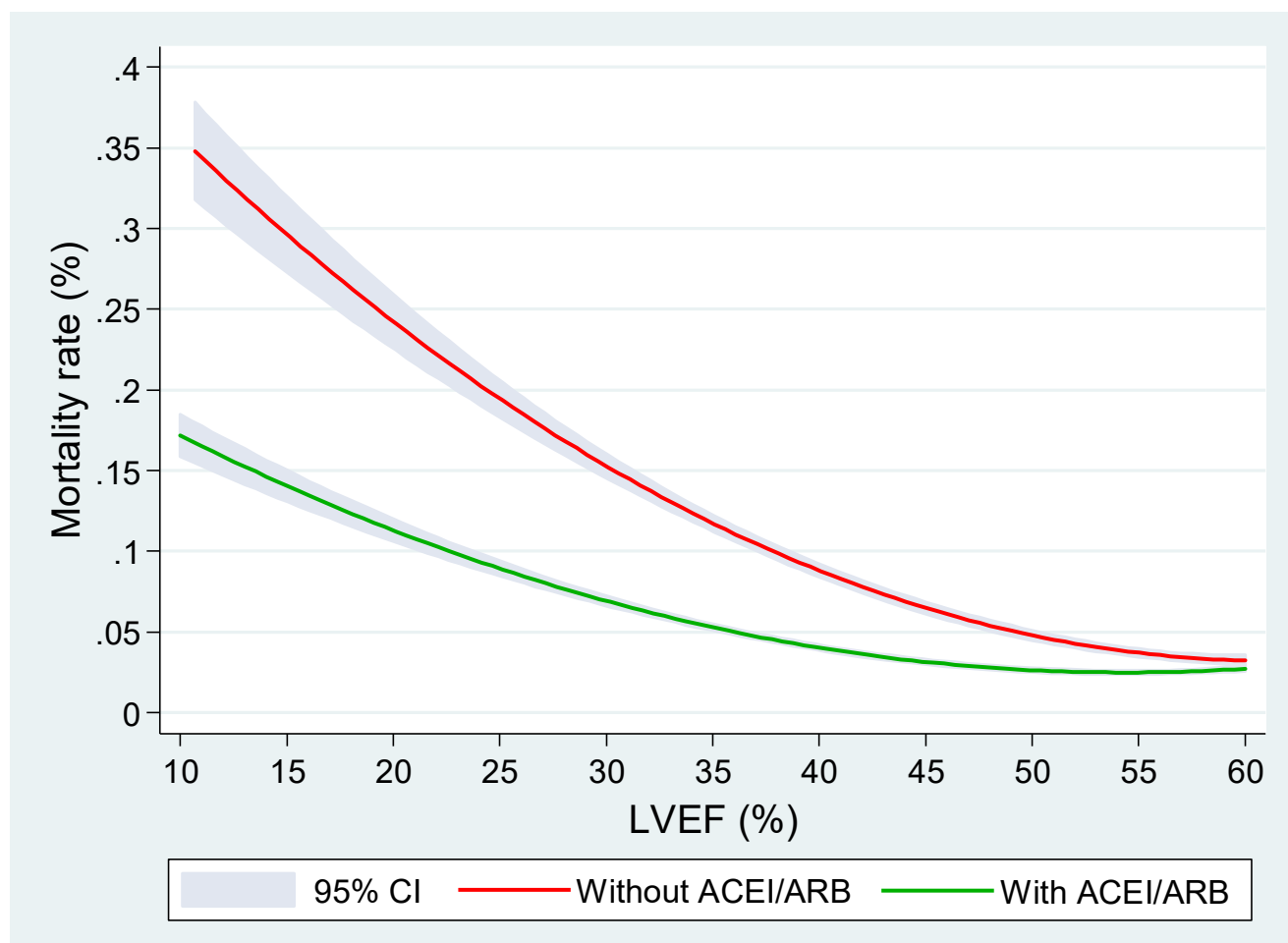
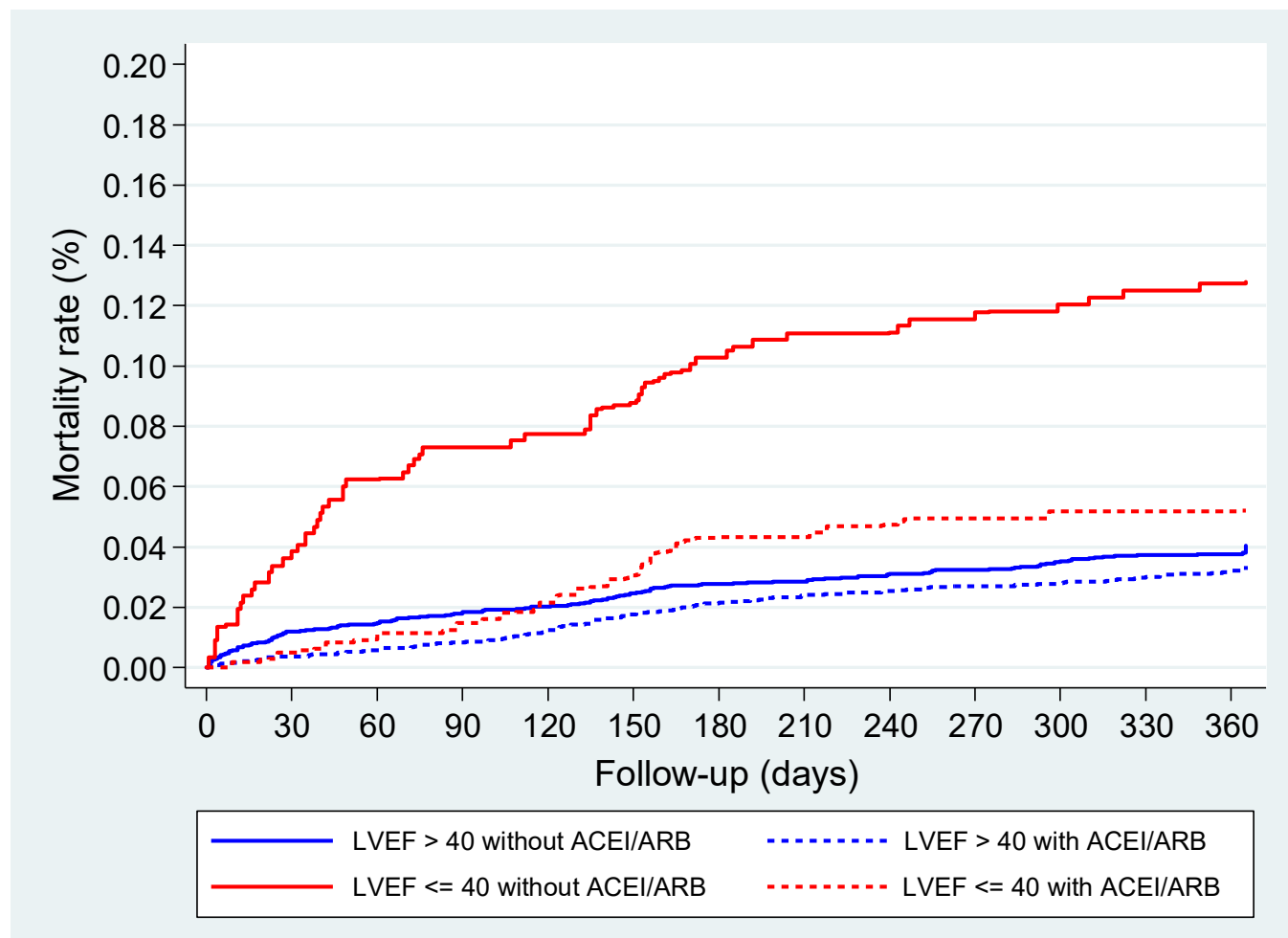


Figure 9

Impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) after propensity score matching on 1-year mortality according to left ventricular ejection fraction (LVEF) as categorical variable (LVEF > 40% vs ≤ 40%).

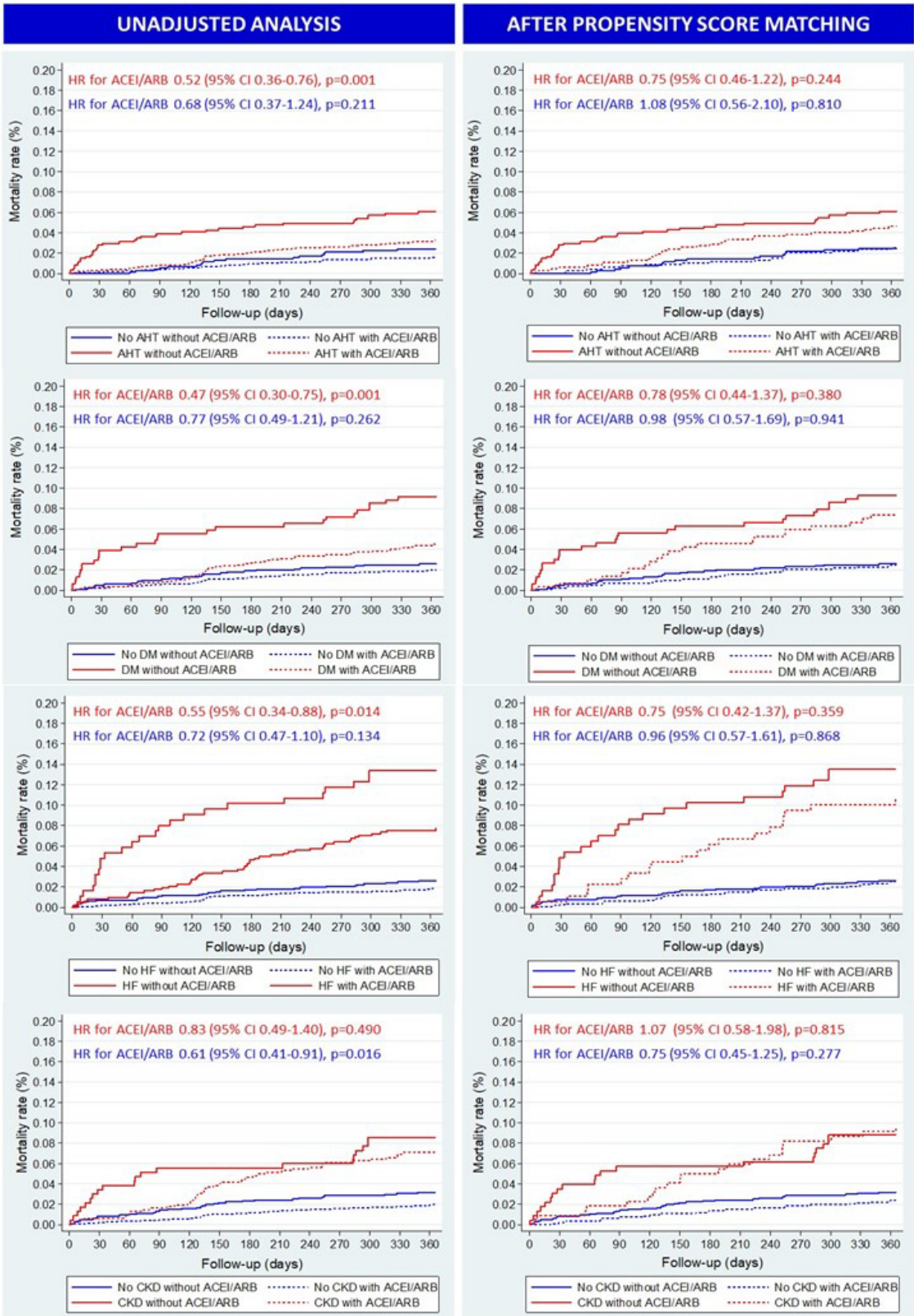


For LVEF > 40% (BLUE): HR, 0.744; 95% CI, 0.494-1.120, $P = .156$

For LVEF ≤ 40% (RED): HR, 0.427; 95% CI, 0.229-0.798, $P = .008$

Figure 10

Impact of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) on 1-year mortality according to risk factors (heart failure [HF]), chronic kidney disease [CKD], diabetes mellitus [DM], and arterial hypertension [AHT]) in patients with left ventricular ejection fraction (LVEF) > 40%.



Correcciones a la figura

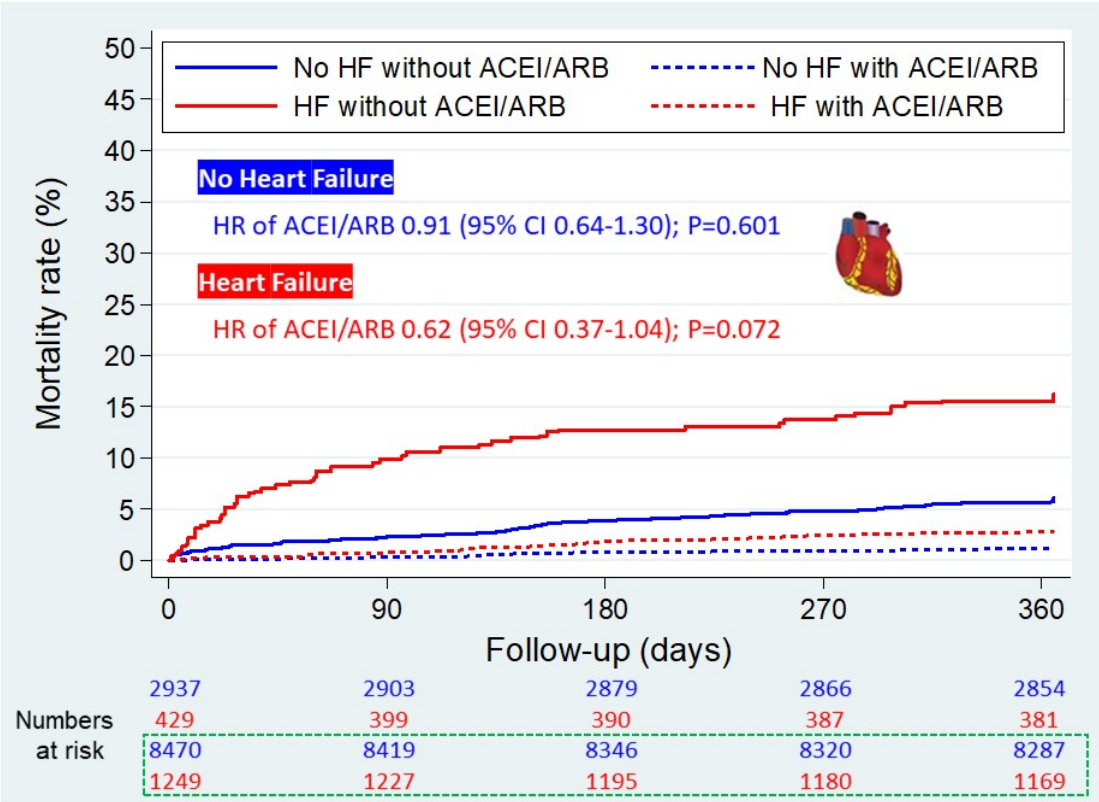
Indicar valores de P en formato REC

ADJUSTED KAPLAN MEIER CURVES

For high-risk conditions (heart failure, renal failure, diabetes mellitus, hypertension)

Figure 11

Adjusted survival Kaplan-Meier curves for the prescription of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) at discharge according to presence or absence of heart failure (HF) in ACS patients with left ventricular ejection fraction > 40%.



Corrección a la figura: indicar valor de P en formato REC

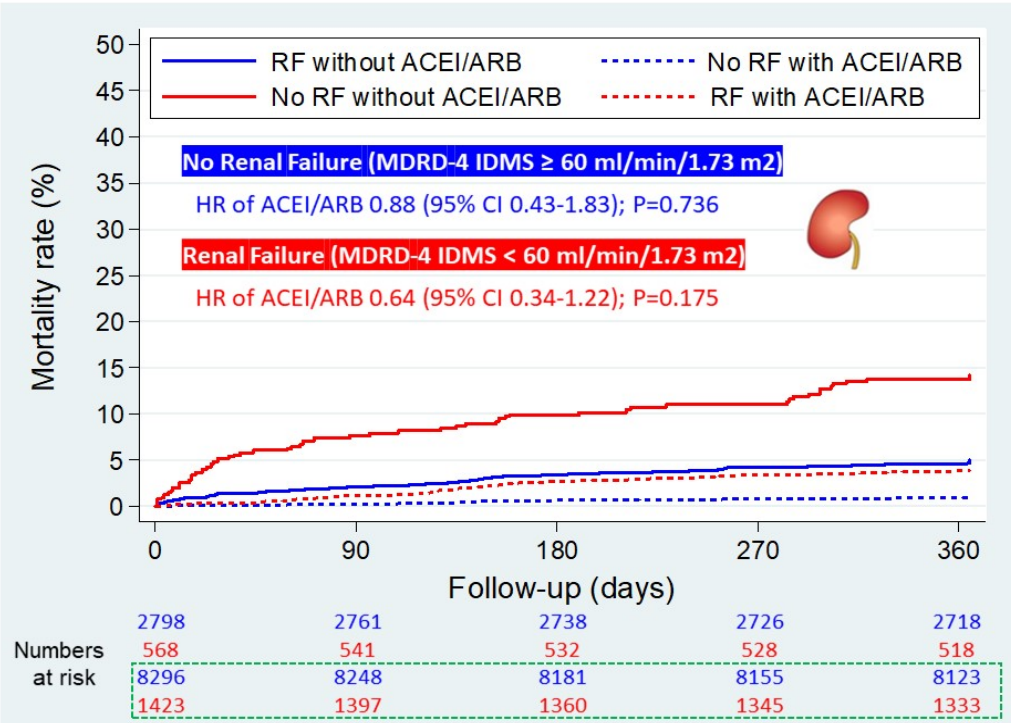
Analyses were adjusted for the inverse weighted propensity (IWP) scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, hypertension, diabetes, dyslipidemia, prior myocardial infarction, prior stroke, renal failure (MDRD-4 IDMS < 60 mL/min/1.73 m²), peripheral artery disease, history of cancer in last 5 years, type of ACS (unstable angina/non-ST-elevation myocardial infarction/ST-elevation myocardial infarction), hemoglobin at admission, multivessel coronary artery disease, drug-eluting stent implantation, complete

revascularization, in-hospital reinfarction, dual antiplatelet therapy at discharge, beta-blocker prescription at discharge, statin prescription at discharge, country of admission, year of admission).

Numbers at risk. Patients without HF are represented in blue and patients with HF in red. Patients treated with ACEI/ARB are represented in the box with the green flashing outline.

Figure 12

Adjusted survival Kaplan-Meier curves for the prescription of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) at discharge according to presence or absence of renal failure (RF) in ACS patients with left ventricular ejection fraction > 40%.



Correcciones a la figura:

No Renal Failure → No renal failure

Renal Failure → Renal failure

ml → mL

Indicar valores de P en formato REC

M2 → m²

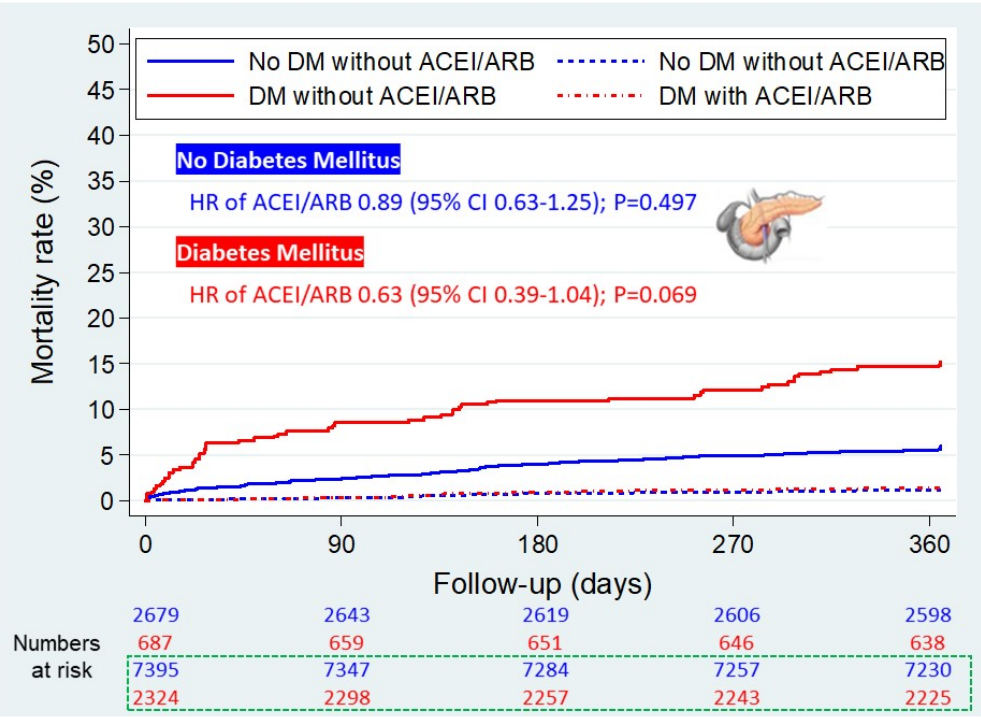
Analyses were adjusted for the IWP scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, diabetes, hypertension, dislipemia, prior myocardial infarction, prior stroke, peripheral artery disease, history of heart failure/Killip class > I at admission or in-hospital heart failure, history of cancer in last 5 years, type of ACS (unstable angina/non-ST-elevation

myocardial infarction/ST-elevation myocardial infarction), hemoglobin at admission, multivessel coronary artery disease, drug-eluting stent implantation, complete revascularization, in-hospital reinfarction, dual antiplatelet therapy at discharge, beta-blocker prescription at discharge, statin prescription at discharge, country of admission, year of admission).

Numbers at risk. Patients without RF are represented in blue and patients with RF in red. Patients treated with ACEI/ARB are represented in the box with green flashing outline.

Figure 13

Adjusted survival Kaplan-Meier curves for the prescription of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) at discharge according to presence or absence of diabetes (DM) in ACS patients with left ventricular ejection fraction > 40%.



Correcciones a la figura:

No Diabetes Mellitus -> No diabetes mellitus

Diabetes Mellitus -> Diabetes mellitus

Indicar valores de P en formato REC

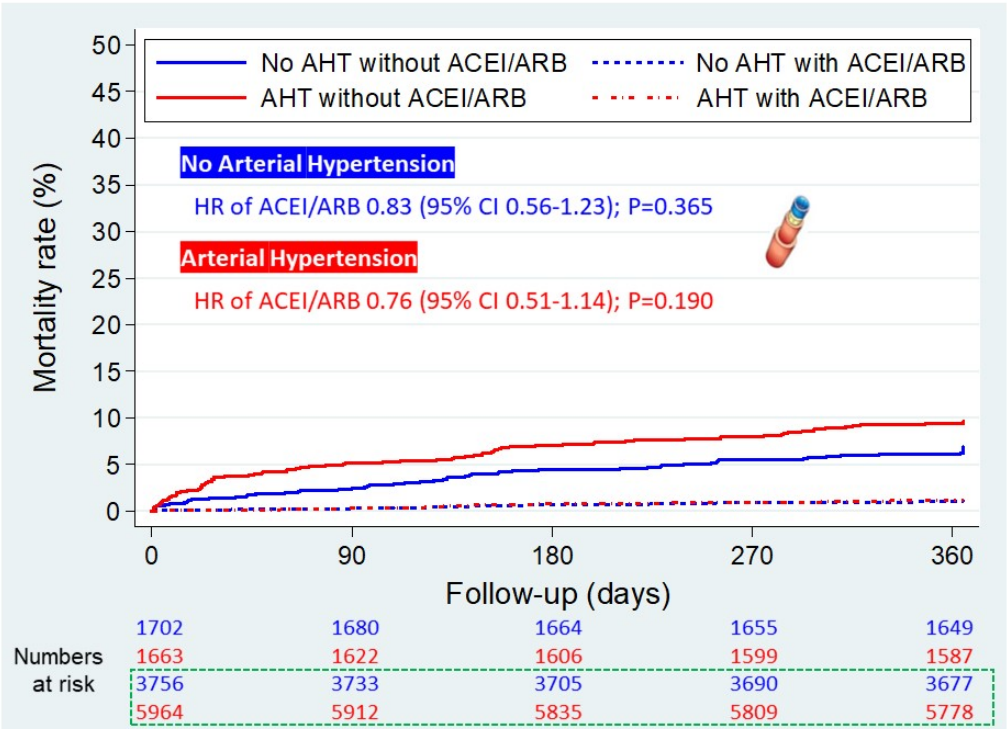
Analyses were adjusted for the IWP scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, hypertension, dislipemia, prior myocardial infarction, prior stroke, renal failure (MDRD-4 IDMS < 60 mL/min/1.73 m²), peripheral artery disease, history of heart failure/Killip class > I at admission or in-hospital heart failure, history of cancer in last 5 years, type of ACS (unstable angina/non-ST-elevation myocardial infarction/ST-elevation myocardial

infarction), hemoglobin at admission, multivessel coronary artery disease, drug-eluting stent implantation, complete revascularization, in-hospital reinfarction, dual antiplatelet therapy at discharge, beta-blocker prescription at discharge, statin prescription at discharge, country of admission, year of admission).

Numbers at risk. Patients without DM are shown in blue and patients with DM in red. Patients treated with ACEI/ARB are represented in the box with the green flashing outline.

Figure 14

Adjusted survival Kaplan-Meier curves for the prescription of angiotensin converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) at discharge according to presence or absence of arterial hypertension (AHT) in ACS patients with left ventricular ejection fraction > 40%.



Correcciones a la figura:

No Arterial Hypertension -> No arterial hypertension

Arterial Hypertension -> Arterial hypertension

Indicar valores de P en formato REC

Analyses were adjusted for the IWP scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, diabetes, dislipidemia, prior myocardial infarction, prior stroke, renal failure (MDRD-4 IDMS < 60 mL/min/1.73 m²), peripheral artery disease, history of heart failure/Killip class > I at admission or in-hospital heart failure, history of cancer in last 5 years, type of ACS (unstable angina/non-ST-elevation myocardial infarction/ST-elevation myocardial infarction), hemoglobin at admission, multivessel coronary artery disease, drug-eluting stent implantation, complete

revascularization, in-hospital reinfarction, dual antiplatelet therapy at discharge, beta-blocker prescription at discharge, statin prescription at discharge, country of admission, year of admission).

Numbers at risk. Patients without AHT are represented in blue and patients with AHT in red. Patients treated with ACEI/ARB are represented in the box with green flashing outline.