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 (≥ 50% in left main coronary artery, ≥ 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 ClincalTrial.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 (≥ 50% in left main coronary artery, ≥ 70% in the rest of the coronary arteries) during the index entry by ACS.
3. Performance of PCI during the index entry for ACS.

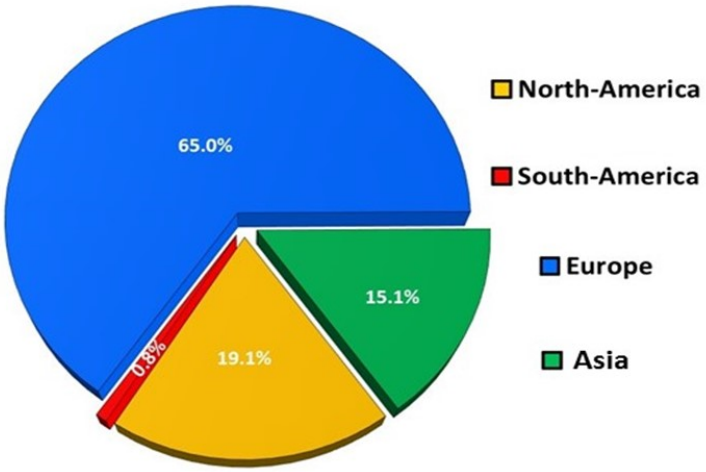
3. VARIABLES INCLUDED IN THE BleeMACS REGISTRY

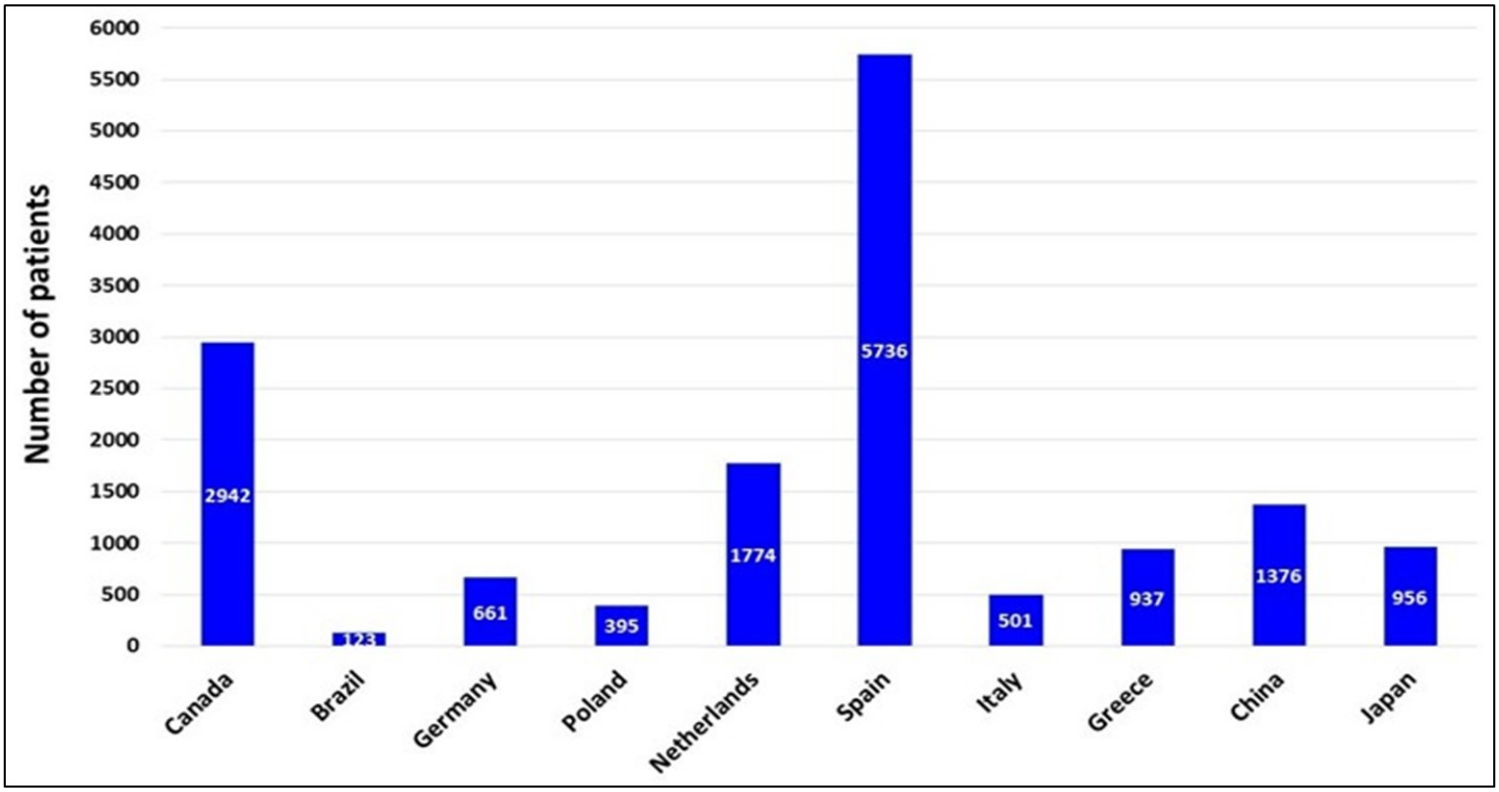
- Demographic variables: Date of admission (date variable), date of discharge (date variable), date of birth (date variable), age (continuous variable, years), sex (male or female).
- Baseline characteristics: Diabetes mellitus (yes/no), arterial hypertension (yes/no), dyslipidemia (yes/no), history 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 ≥ 70%), left coronary artery stenosis ≥ 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.

CONTINENT	HOSPITAL	TIME PERIOD	N
EUROPE	Clinical Hospital of Santiago de Compostela, Spain	2004-2012	3134
	Bellvitge Hospital, Spain	2011-2013	1438
	Hospital San Carlos, Spain	2009-2012	1164
	Academic Medical Center, Amsterdam, Netherlands	2003-2008	1774
	University Patras Hospital, Greece	2012-2013	937
	Kerckhoff Heart and Thorax Center, Frankfurt, Germany	2010-2013	661
	CInical Hospital, Varsaw, Poland	2010-2011	395
	San Giovanni Battista Molinette Hospital, Turin, Italy	2005-2006	501
NORTH-AMERICA	Libin Cardiovascular Institute of Alberta, Canada	2005-2011	2942
SOUTH-AMERICA	Hospital Sao Rafael, Salvador, Brazil	2010-2012	123
ASIA	University Graduate School of Medicine, Kyoto, Japan	2004-2011	600
	Tokai University School of Medicine, Tokai, Japan	2012	112
	University Graduate School of Medicine, Kanazawa, Japan	2007-2012	244
	Anzhen Hospital, Beijing, China	2006-2012	1059
	Capital Medical University, Beijing, China	2014	317





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

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

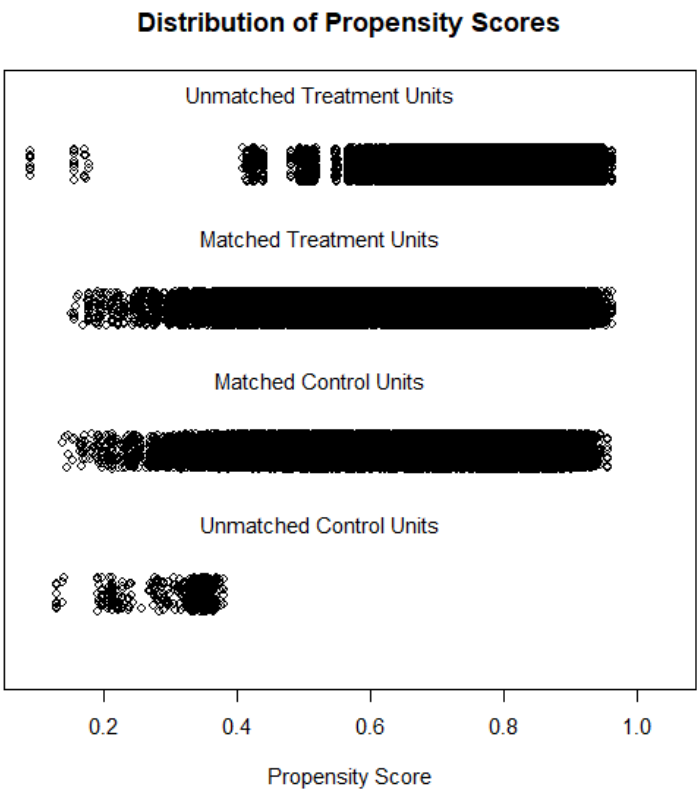
Subsamples	Covariates	Means treated		Means control		SD control		Std. mean diff.	
		Before	After	Before	Before	After	After	Before	After
(all cases)	propensity	0.776	0.697	0.678	0.812	0.108	0.148	0.812	0.108
	Age	63.688	63.263	63.490	0.016	−0.015	12.944	0.016	−0.015
	Female sex	0.226	0.250	0.254	−0.067	−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 diseasse	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

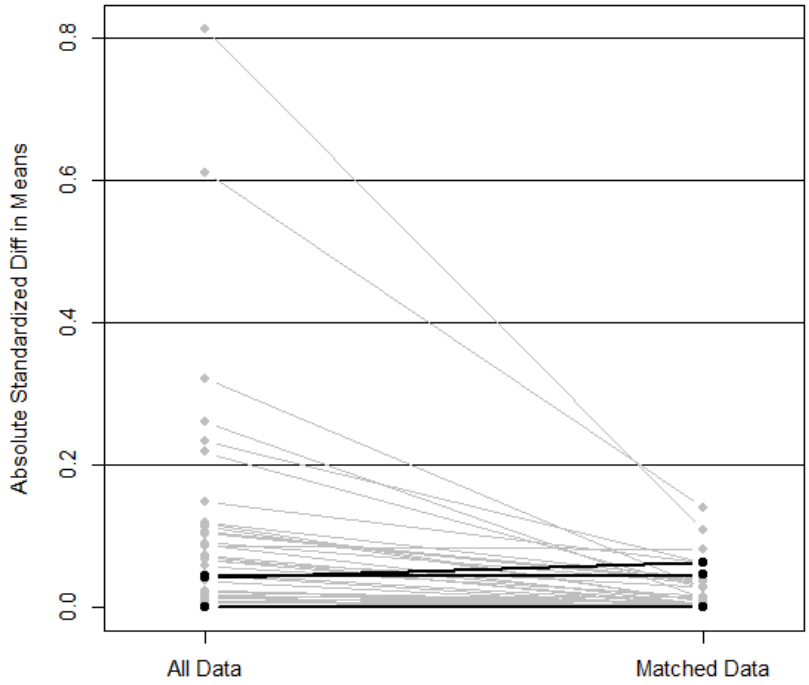
Matched Control Units -> Matched control units

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.

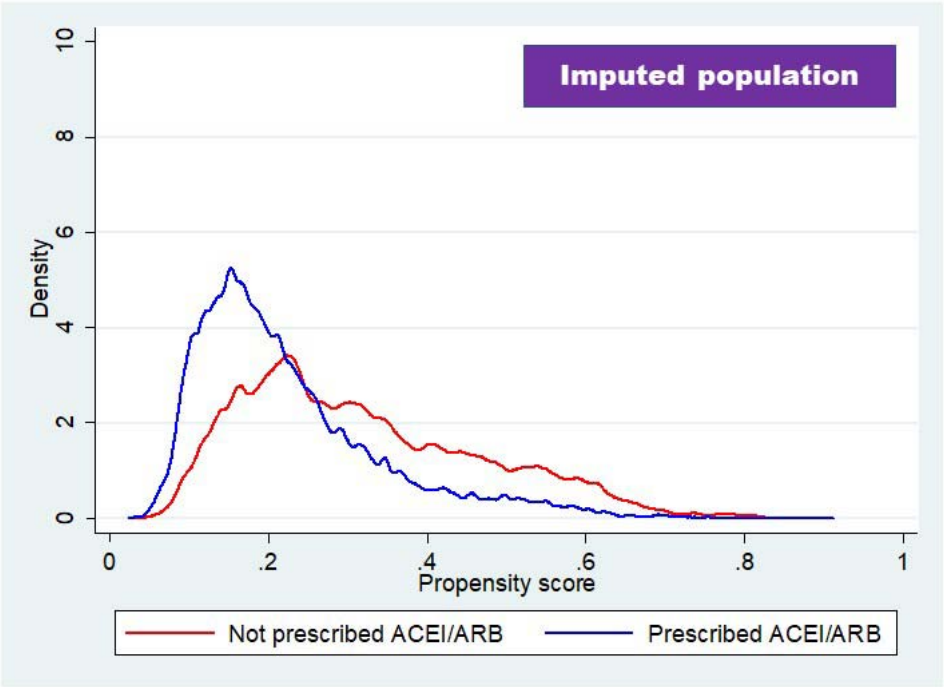
Augmented inverse probability weights (AIPW)

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

Tto 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 as 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 ± 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

Table 4

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

Dataset 1				
Total	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.008	0.015 to −0.001	.034
	Instrumental variable	Coefficient	95% CI	*P*
		−0.232	−0.326 to −0.138	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.027	−0.055 to 0.002	.066
	Instrumental variable	Coefficient	95% CI	*P*
		−0.470	−0.668 to −0.273	< .001
LVEF > 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.005	−0.012 to 0.002	.152
	Instrumental variable	Coefficient	95% CI	*P*
		−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 ≥ 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	*P*
	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	*P*
		−0.008	−0.015 to −0.001	.034
	Instrumental variable	Coefficient	95% CI	*P*
		−0.233	−0.327 to −0.139	<.001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.029	−0.059 to 0.001	.056
	Instrumental variable	Coefficient	95% CI	*P*
		−0.437	−0.639 to −0.236	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		−0.006	−0.013 to 0.001	.111
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.009	−0.016 to −0.001	.021
	Instrumental variable	Coefficient	95% CI	*P*
		-0.236	−0.329 to −0.142	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.024	−0.050 to 0.028	.079
	Instrumental variable	Coefficient	95% CI	*P*
		-0.479	−0.680 to −0.278	<0.001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		-0.006	−0.013 to 0.001	.084
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.008	−0.016 to −0.001	.031
	Instrumental variable	Coefficient	95% CI	*P*
		−0.236	−0.330 to −0.143	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.022	−0.050 to 0.006	.123
	Instrumental variable	Coefficient	95% CI	*P*
		−0.443	−0.646 to −0.239	< .001
LVEF > 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.006	−0.014 to 0.001	.080
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.008	−0.016 to −0.001	.029
	Instrumental variable	Coefficient	95% CI	*P*
		−0.242	−0.336 to −0.149	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.025	−0.055 to 0.005	.112
	Instrumental variable	Coefficient	95% CI	*P*
		−0.467	−0.667 to −0.266	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		−0.006	−0.013 to 0.001	.106
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		-0.008	−0.015 to −0.001	.032
	Instrumental variable	Coefficient	95% CI	*P*
		-0.237	−0.330 to −0.143	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.026	−0.055 to 0.002	.067
	Instrumental variable	Coefficient	95% CI	*P*
		−0.453	−0.656 to −0.244	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		-0.005	−0.013 to 0.001	.101
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		-0.008	−0.016 to −0.001	.029
	Instrumental variable	Coefficient	95% CI	*P*
		-0.233	−0.327 to −0.140	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.033	−0.062 to −0.002	.032
	Instrumental variable	Coefficient	95% CI	*P*
		−0.486	−0.684 to −0.287	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		−0.005	−0.012 to 0.002	.137
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.008	−0.015 to −0.001	.034
	Instrumental variable	Coefficient	95% CI	*P*
		−0.234	−0.328 to −0.140	<.001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.028	−0.056 to 0.001	.055
	Instrumental variable	Coefficient	95% CI	*P*
		−0.467	−0.668 to −0.266	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		−0.005	−0.012 to 0.002	.162
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.007	−0.015 to 0.001	.051
	Instrumental variable	Coefficient	95% CI	*P*
		−0.234	−0.327 to −0.140	< .001
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.026	−0.053 to 0.001	.061
	Instrumental variable	Coefficient	95% CI	*P*
		−0.482	−0.689 to −0.274	< .001
EF >	Cox regression	HR	95% CI	*P*

	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	*P*
		−0.005	−0.012 to 0.002	.166
	Instrumental variable	Coefficient	95% CI	*P*
		−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	*P*
	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	*P*
		−0.007	−0.015 to −0.001	.047
	Instrumental variable	Coefficient	95% CI	*P*
		−0.228	−0.321 to −0.054	.003
LVEF ≤ 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.023	−0.051 to 0.006	.117
	Instrumental variable	Coefficient	95% CI	*P*
		−0.432	−0.637 to −0.226	< .001
LVEF > 40	Cox regression	HR	95% CI	*P*
	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	*P*
		−0.006	−0.013 to 0.001	.109
	Instrumental variable	Coefficient	95% CI	*P*
		−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

Variables	ACEI/ARB at hospital discharge* 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 ≥ II	14.2	12.3	.012	3324 (21.6%)
Left ventricular ejection fraction ≤ 40%, %	16.7	13.3	< .001	5305 (34.4%)
Hemoglobin at admission, g/dL	14.0 ± 1.8	13.8 ± 1.8	< .001	1297 (8.4%)
Creatinine at admission, mg/dL	0.9 ± 0.4	1.0 ± 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 ± standard deviation.

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

Table 15

Detailed balance of propensity score matching

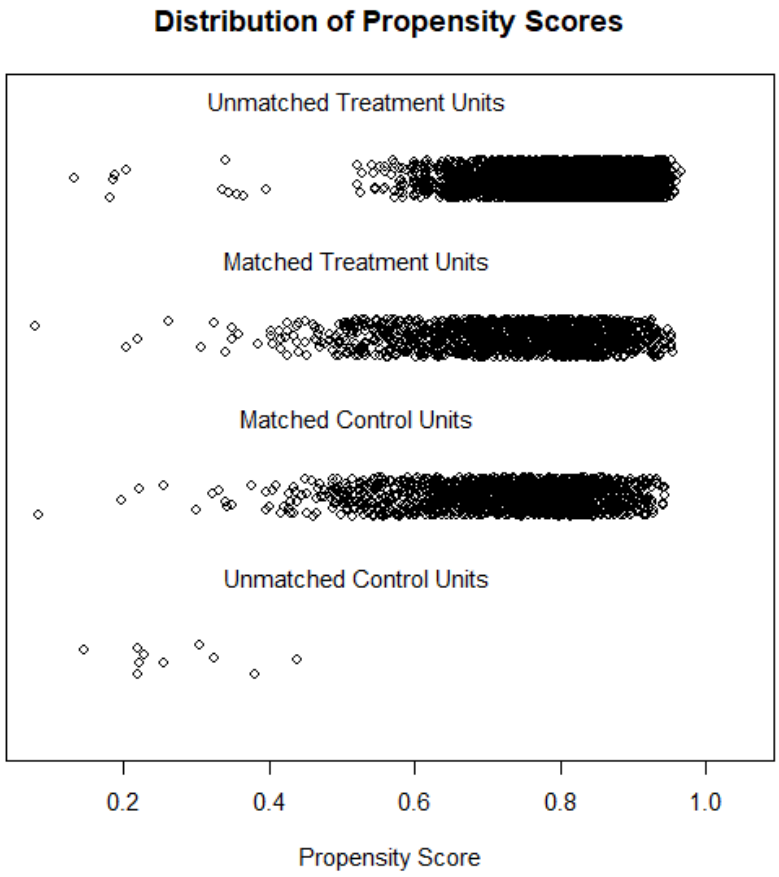
		Means treated		Means control		SD control		Std. mean diff.	
Subsamples	Covariates	Before	After	Before	After	Before	After	Before	After
(all cases)	propensity	0.800	0.744	0.730	0.733	0.123	0.117	0.691	0.104
	Age	63.946	63.648	63.918	63.858	13.488	13.473	0.002	−0.017
	Female	0.216	0.230	0.234	0.232	0.423	0.422	−0.042	−0.005
	Year	2009.291	2008.738	2008.691	2008.698	2.737	2.738	0.231	0.015
	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	−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 anticoagultion	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

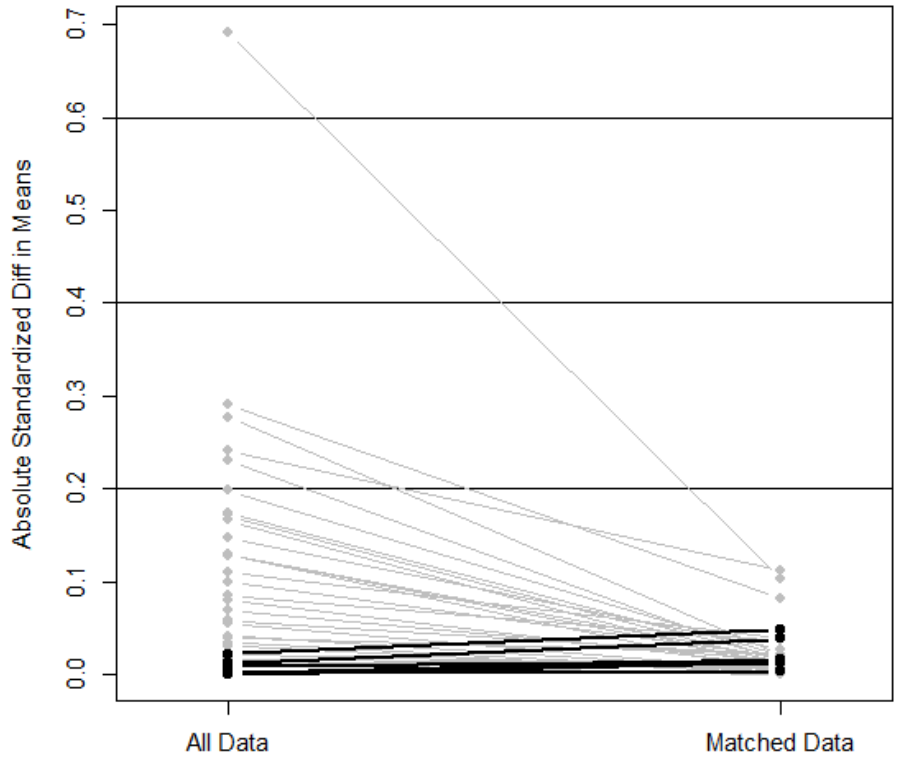
Matched Treatment Units → Matched treatment units

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

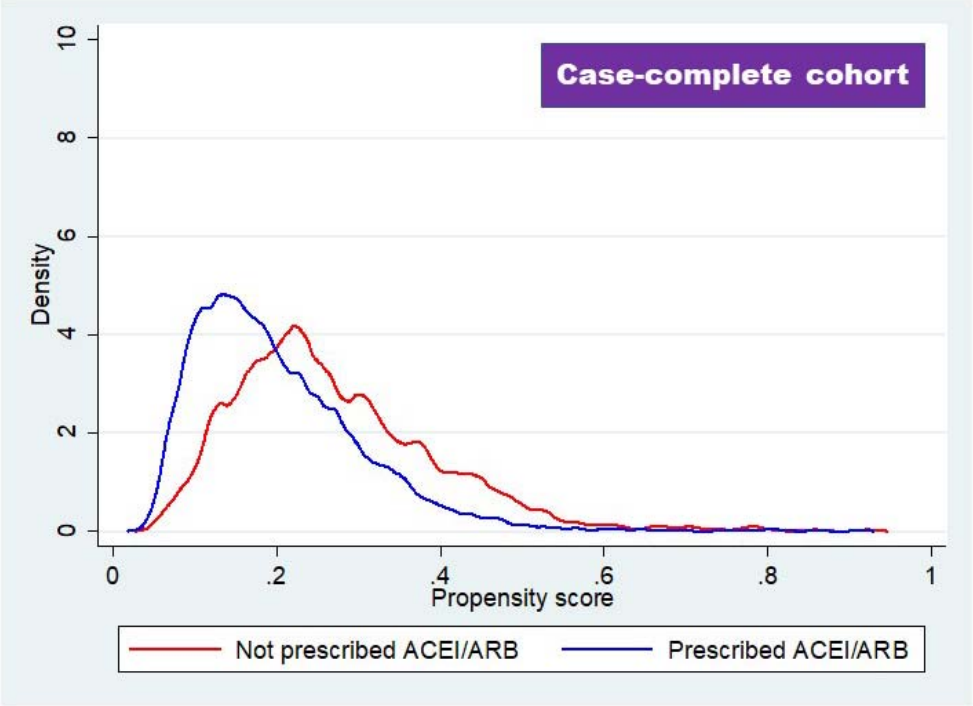
Absolute Standardized Diff in Means → Absolute standardized mean differences

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	*P*
		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	*P*
		ATE (risk difference)	-0.010	−0.021 to 0.002	.094
		Instrumental Variable	Coefficient	95% CI	*P*
		Relative risk reduction	-0.295	−0.440 to −0.150	< .001
Subgroups by	**LVEF**	Cox Regression	HR	95% CI	HR
	LVEF ≤ 40	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	*P*
		ATE (risk difference)	−0.025	−0.063 to 0.013	.197
		Instrumental variable	Coefficient	95% CI	*P*
		Relative risk reduction	−0.452	−0.728 to −0.174	.001
	LVEF > 40	Cox regression	HR	95% CI	*P*
		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	*P*
		ATE (risk difference)	−0.009	−0.020 to 0.019	.107
		Instrumental variable	Coefficient	95% CI	*P*
		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 ≥ 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).

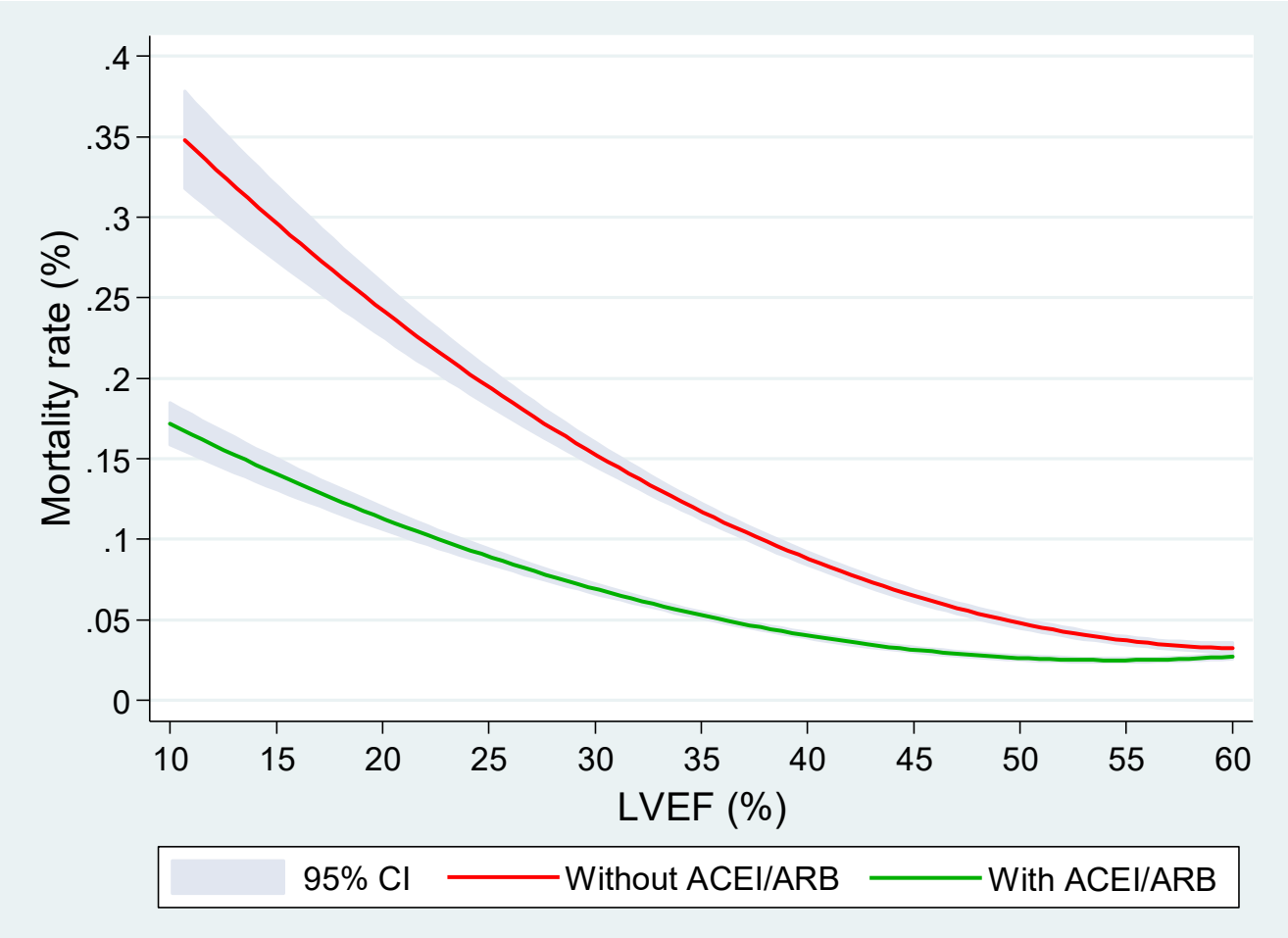
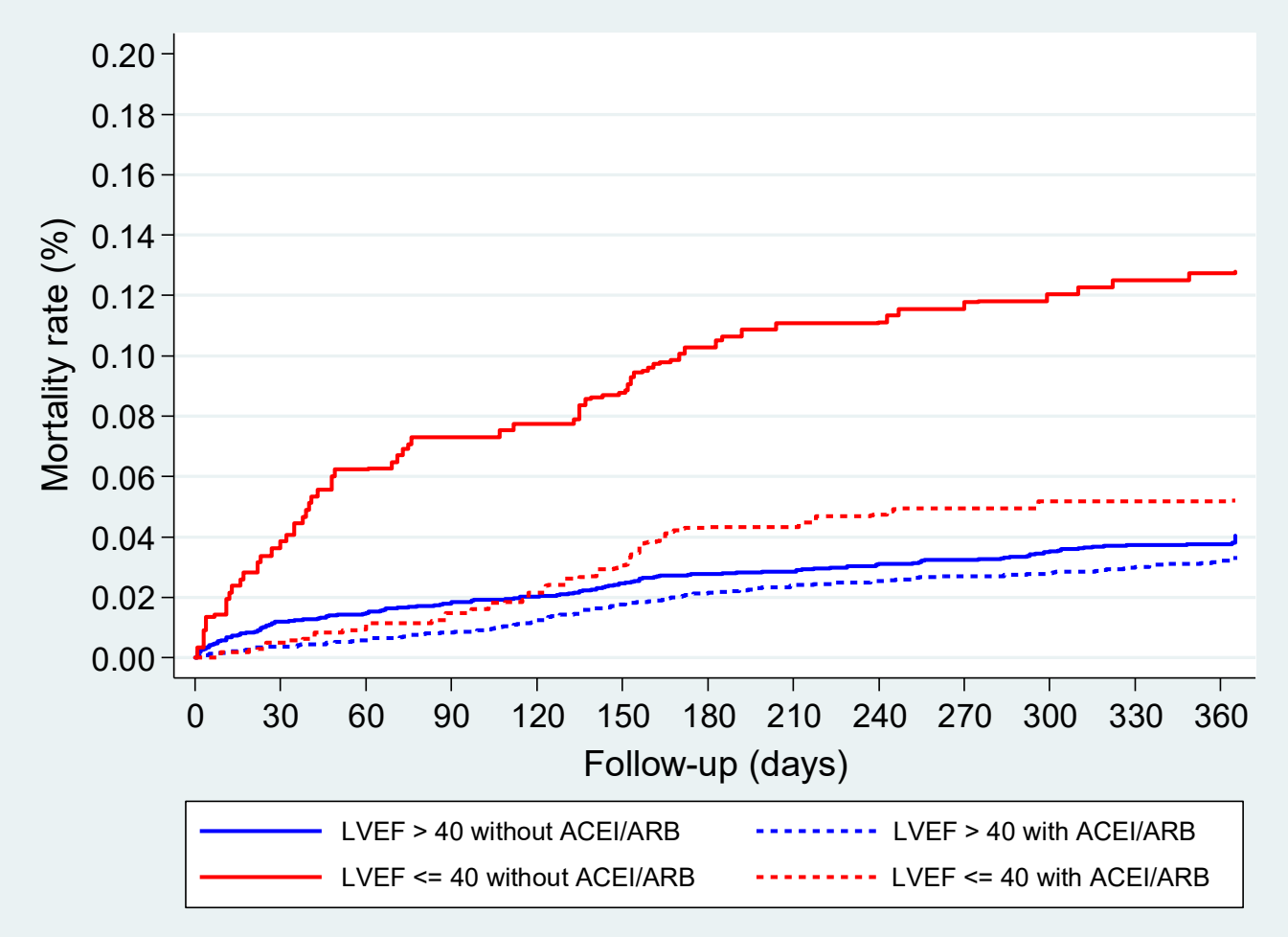


Figure 9

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%).

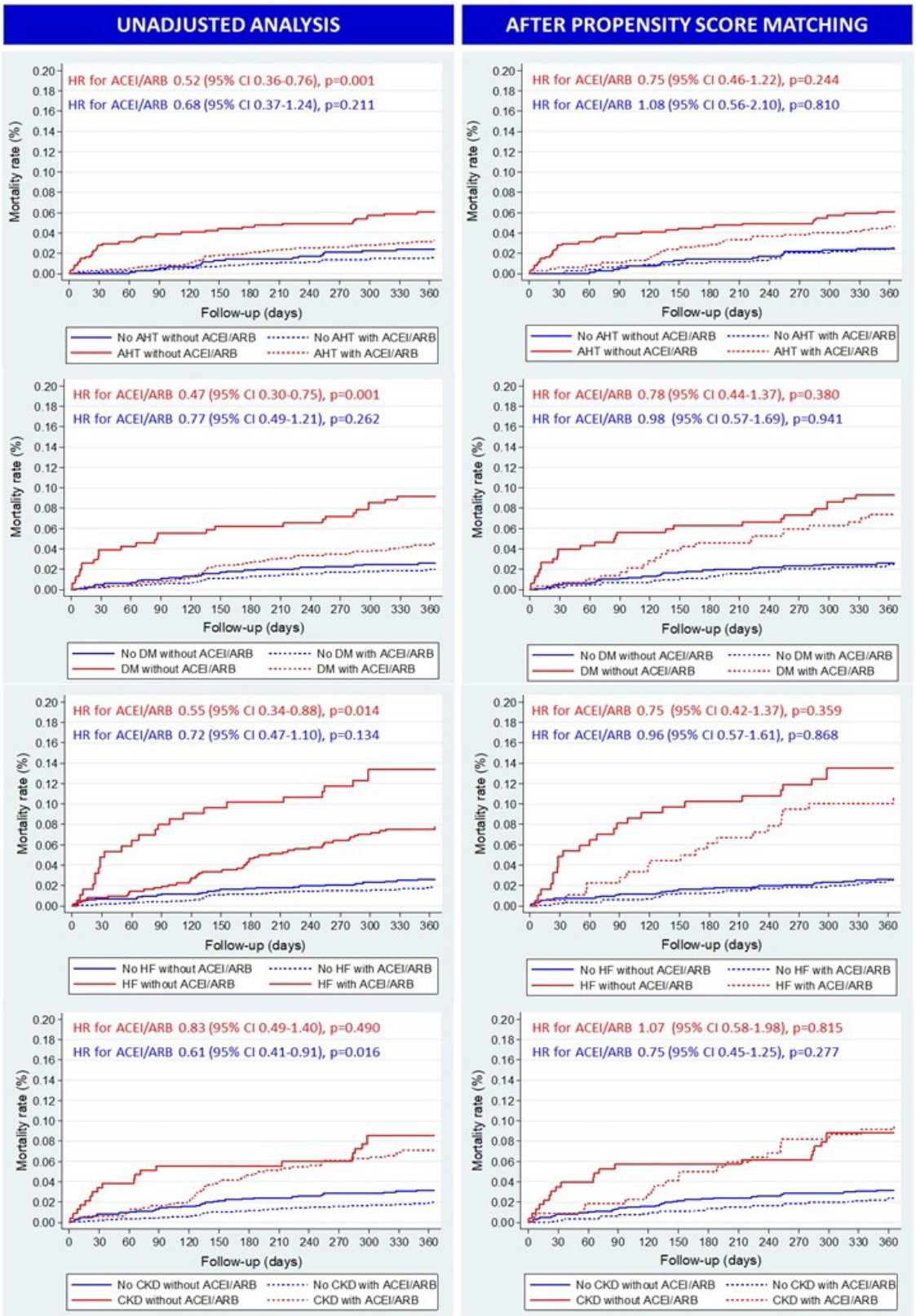


For LVEF > 40% (BLUE): HR, 0.744; 95% CI, 0.494-1.120, *P* = .156

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

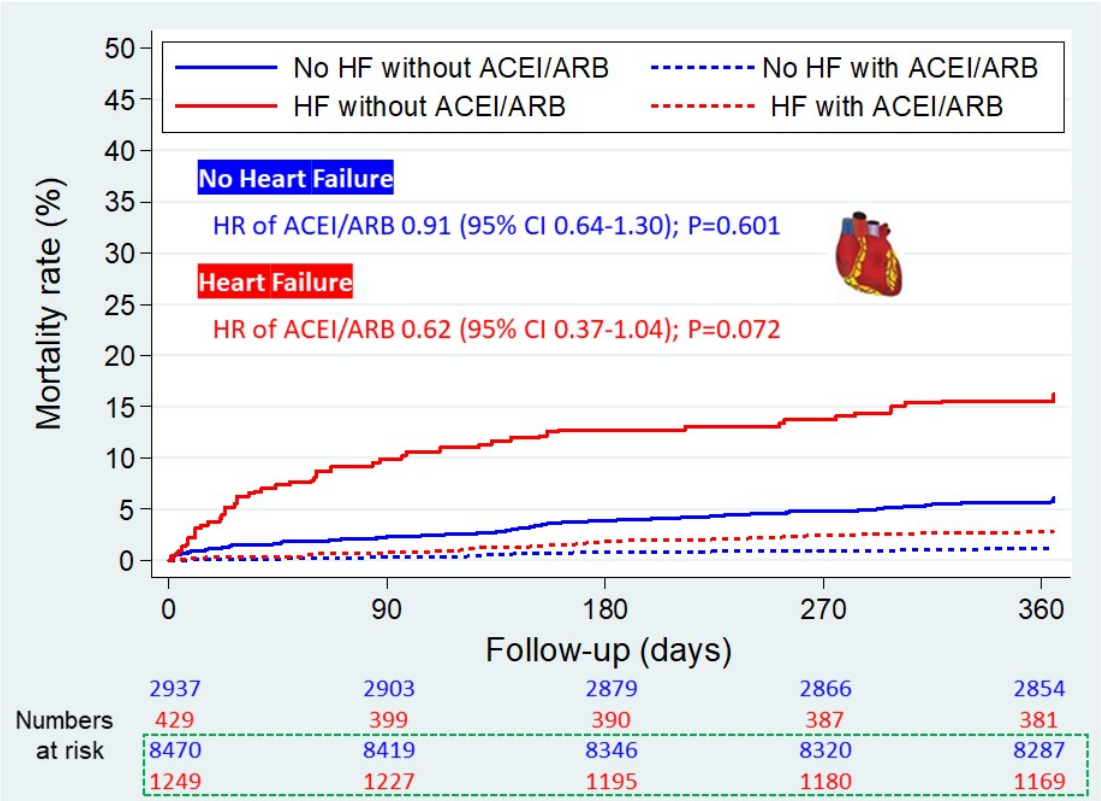
Indicar valores de P en formato REC

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

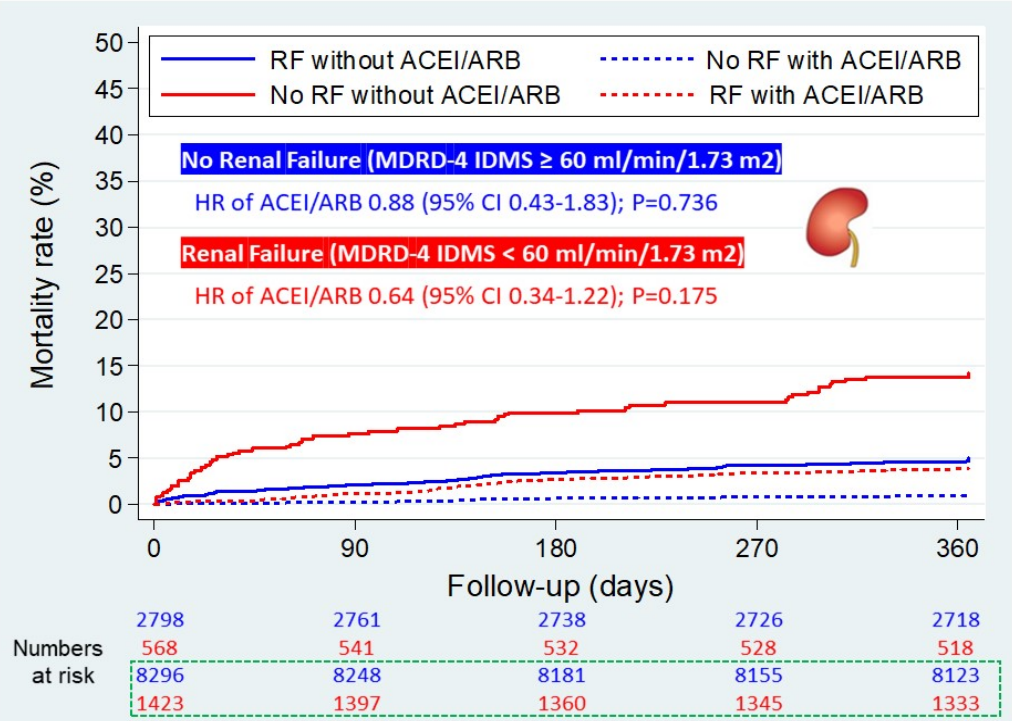
Analyses were adjusted for the inverse weighted propensity (IWP) scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, hypertension, diabetes dislipemia, prior myocardial infarction, prior stroke, renal failure (MDRD-4 IDMS < 60 mL/min/1.73 m^2), 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 → m^2

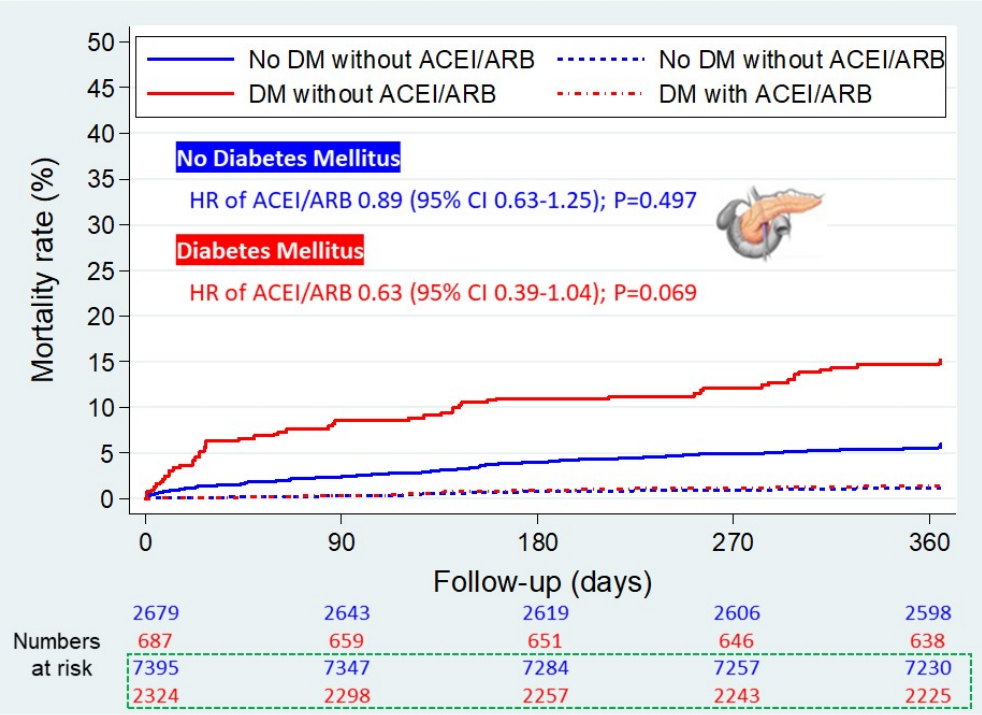
Analyses were adjusted for the IWP scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, diabetes, hypertension, dislipemia, prior myocardial infarction, prior stroke, peripheral artery disease, history of heart failure/Killip class > I 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

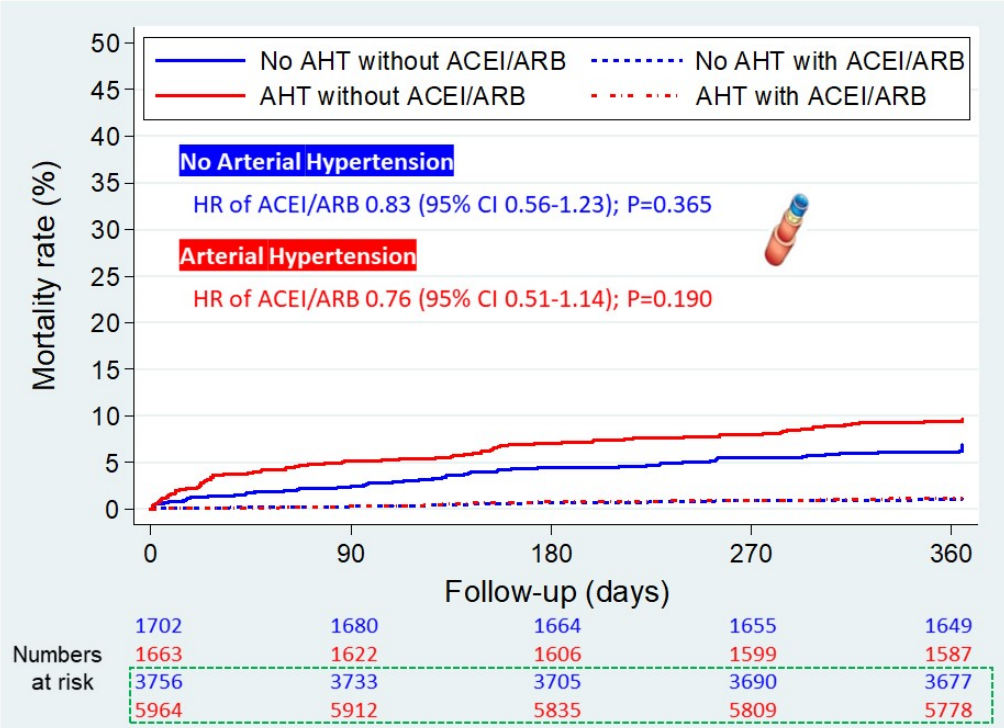
Analyses were adjusted for the IWP scores of receipt of care and covariates associated with 1-year mortality in the univariate analysis (age, female sex, hypertension, dislipemia, prior myocardial infarction, prior stroke, renal failure (MDRD-4 IDMS < 60 mL/min/1.73 m^2), peripheral artery disease, history 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 m^2), 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.