



Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease

Editorial, see p 1490

BACKGROUND: Myocardial infarction with nonobstructive coronary arteries (MINOCA) occurs in 5% to 10% of all patients with myocardial infarction. Clinical trials of secondary prevention treatment in MINOCA patients are lacking. Therefore, the aim of this study was to examine the associations between treatment with statins, renin-angiotensin system blockers, β -blockers, dual antiplatelet therapy, and long-term cardiovascular events.

METHODS: This is an observational study of MINOCA patients recorded in the SWEDEHEART registry (the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy) between July 2003 and June 2013 and followed until December 2013 for outcome events in the Swedish Cause of Death Register and National Patient Register. Of 199 162 myocardial infarction admissions, 9466 consecutive unique patients with MINOCA were identified. Among those, the 9136 patients surviving the first 30 days after discharge constituted the study population. Mean age was 65.3 years, and 61% were women. No patient was lost to follow-up. A stratified propensity score analysis was performed to match treated and untreated groups. The association between treatment and outcome was estimated by comparing between treated and untreated groups by using Cox proportional hazards models. The exposures were treatment at discharge with statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, and dual antiplatelet therapy. The primary end point was major adverse cardiac events defined as all-cause mortality, hospitalization for myocardial infarction, ischemic stroke, and heart failure.

RESULTS: At discharge, 84.5%, 64.1%, 83.4%, and 66.4% of the patients were on statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β -blockers, and dual antiplatelet therapy, respectively. During the follow-up of a mean of 4.1 years, 2183 (23.9%) patients experienced a major adverse cardiac event. The hazard ratios (95% confidence intervals) for major adverse cardiac events were 0.77 (0.68–0.87), 0.82 (0.73–0.93), and 0.86 (0.74–1.01) in patients on statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and β -blockers, respectively. For patients on dual antiplatelet therapy followed for 1 year, the hazard ratio was 0.90 (0.74–1.08).

CONCLUSIONS: The results indicate long-term beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on outcome in patients with MINOCA, a trend toward a positive effect of β -blocker treatment, and a neutral effect of dual antiplatelet therapy. Properly powered randomized clinical trials to confirm these results are warranted.

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Clinical Perspective

What Is New?

- This is the first study evaluating secondary prevention treatments in a large group of patients with myocardial infarction with nonobstructive coronary arteries.
- Patients treated with statins and renin-angiotensin system blockers had a significantly 23% and 18% lower risk of a major adverse cardiac event during follow-up.
- In contrast, there were no significant reductions in risk of major adverse cardiac events after treatment with β -blockers and dual antiplatelet therapy.

What Are the Clinical Implications?

- The results indicate that long-term treatment with statins and renin-angiotensin system blockers may be beneficial in patients with myocardial infarction with nonobstructive coronary arteries.
- Treatment with β -blockers and dual antiplatelet therapy seem less likely to reduce the risk of new cardiovascular events in patients with myocardial infarction with nonobstructive coronary arteries.

It is increasingly recognized that a group of patients diagnosed with myocardial infarction (MI) have no angiographically obstructive ($\geq 50\%$ diameter stenosis) coronary artery disease (CAD) and the term myocardial infarction with nonobstructive coronary arteries (MINOCA) has been coined for this entity.^{1,2} MINOCA occurs in 5% to 10% of all patients with acute MI and these patients are younger and more often women in comparison with patients with MI and obstructive CAD.^{3,4} The underlying pathophysiological mechanisms are poorly understood, although several different mechanisms have been proposed, including plaque disruption, spasm, thromboembolism, dissection, microvascular dysfunction, ischemic myocardial injury attributable to supply/demand mismatch, and clinically nondetected myocarditis or Takotsubo cardiomyopathy.^{2,5} The effects of secondary preventive treatments proven beneficial in patients with classical type 1 MI are unknown in MINOCA patients; randomized clinical trials, and large observational studies, as well, evaluating different treatments in MINOCA patients do not exist. Hence, evidence-based guidelines for treatment of MINOCA are lacking. Elucidating the associations between different treatments and outcome may also increase the understanding of underlying mechanisms of MINOCA.

All patients in Sweden with MI, in whom coronary angiography is performed, are registered in the SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy).^{6,7} By merging data from the SWEDEHEART registry with

data from the mandatory National Board of Health and Welfare's Cause of Death Register and National Patient Register, we have the unique possibility of long-term follow-up regarding mortality and morbidity in a large number of patients with MINOCA.

Therefore, we aimed to examine the associations between treatment with dual antiplatelet therapy (DAPT), statins, renin-angiotensin system blockers (angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs]), β -blockers, and long-term cardiovascular events.

METHODS

Patients

We identified 9466 unique patients with MINOCA among the 199162 acute MI admissions recorded in the SWEDEHEART registry between July 1, 2003, and June 30, 2013. Patients were identified as having MINOCA if the discharge diagnosis was acute MI (*International Classification of Diseases, 10th Revision* code: I21-I22) and a coronary angiography performed during the index hospitalization did not show a stenosis of $\geq 50\%$. Because very early deaths are less likely to be preventable by secondary preventive treatments and, conversely, a terminal condition may be the reason to abstain initiation of secondary preventive treatment, we excluded the 330 patients who died within 30 days after discharge. Hence, the study cohort in the present study contained of 9136 patients with MINOCA who had survived the first 30 days after discharge (Figure 1).

Primary and Secondary End Points

The primary end point was major adverse cardiac events (MACE) defined as all-cause mortality, hospitalization for MI, ischemic stroke, and heart failure. Secondary end points were the individual components of the primary end point and, in addition, cardiovascular mortality and hospitalization for a bleeding event. For definition of the end points, see [online-only Data Supplement Table 1](#) for list of *International Classification of Diseases, 10th Revision* codes.

Follow-Up

Follow-up data were available by merging data from the mandatory Swedish Cause of Death Register and the National Patient Register (containing data including *International Classification of Diseases, 10th Revision* codes on all hospital admissions in Sweden) with SWEDEHEART. The merging was performed at the National Board of Health and Welfare in Sweden based on the personal identification number that all Swedish citizens and all permanent residents of Sweden have. Patients were followed for events occurring from 30 days after discharge date to occurrence of death or until December 31, 2013, with a mean follow-up of 4.1 years. For statins, β -blockers, and ACEI/ARBs, the analysis of the association between the respective treatment and outcome was based on the entire follow-up period. However, for DAPT, the analysis was based on 1-year follow-up because the guideline recommendation during the study period for the duration of DAPT after MI was up to 1 year,⁸ and few patients continue on DAPT thereafter.

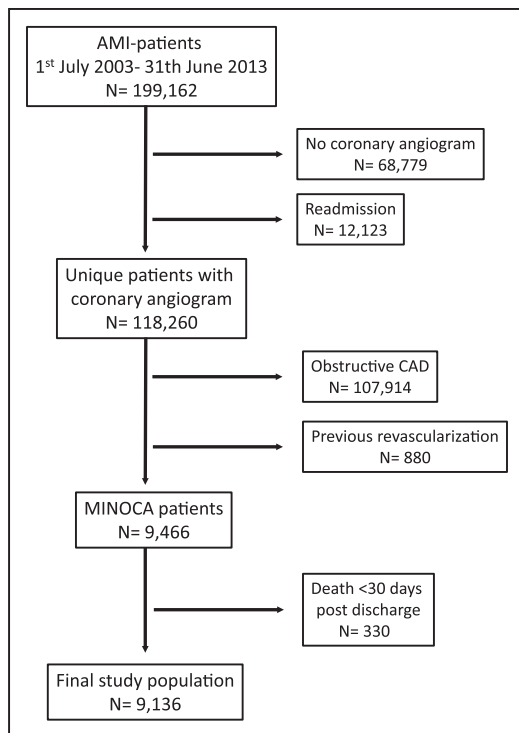


Figure 1. Study population.

AMI indicates acute myocardial infarction; CAD, coronary artery disease; and MINOCA, myocardial infarction with non-obstructive coronary arteries.

The SWEDEHEART registry contains data on baseline characteristics, ECG changes, biochemical markers, coronary angiography results, medical and invasive treatment and outcome (see the SWEDEHEART registry⁷ for details).

To ensure the quality of the data entered into the database, a monitor visit is performed at each hospital every second year. Over the years, there has been a >95% agreement between data in the registry and in the patients' records.⁶

According to Swedish law, all patients must be informed about their participation in the registry and the right to get their data erased from the registry on request. The study was approved by the Regional Ethical Review Board in Stockholm (2012/60-31/2).

Statistics

The statistical methods are described in detail in the [online-only Data Supplement Statistical Methods](#). In summary, categorical variables are presented as frequency values and compared by χ^2 tests. Continuous variables are presented as mean \pm standard deviation. Multiple imputation of missing values of smoking, plasma creatinine, and treatment at admission with ACEI or ARB was performed. A stratified propensity score (PS) analysis was performed to match treated and untreated groups for each separate treatment. Relevant covariates ($n=26$) were entered into a multivariable logistic regression model for each evaluated treatment (see [online-only Data Supplement Table II](#)). The predicted probability derived from the logistic regression equation was used as the PS for each individual. Subjects were then ranked according to their estimated PS. Areas at the extremes of the PS histograms with visually no or very little overlap in PSs between treated and nontreated was removed⁹ (see [online-only Data](#)

[Supplement Figure I](#)) and then 4 equal-size strata were formed, using the quartiles of the estimated PSs. Within each stratum, the association between treatment and outcome was estimated by comparing treated and untreated subjects using Cox proportional hazards models with adjustment for discharge medications. The stratum-specific estimates of hazard ratios (HRs) were pooled across strata to estimate an overall association by using a fixed-effects model. Results are presented as HRs and 95% confidence intervals (CIs) by strata and overall. Pooled HRs were calculated in the total study population and in subgroups based on age and sex. In a post hoc analysis regarding the association between ACEI/ARB and MACE in patients with available echocardiographic data, we included left ventricular ejection fraction in the Cox proportional hazards model. In addition, we estimated the associations between the different treatments and outcome using 1:1 PS matching. We also used the 1:1 matched populations for producing survival curves regarding MACE for treated and nontreated patients by using the Kaplan-Meier method.

All analyses were performed using SAS Software Version 9.4 (SAS Institute) and R (version 3.2.2).

RESULTS

The clinical characteristics and medication at admission of the 9136 patients with MINOCA are shown in Table 1; the mean age was 65.6 (standard deviation 11.5) years, and 61% were women. At discharge, 83.4%, 64.1%, 84.5%, and 66.4% of the patients were on β -blockers, ACEI/ARB, statins, and DAPT, respectively. During the follow-up of a mean of 4.1 years, 2183 (23.9%) patients experienced a MACE, 1222 (13.4%) patients died, 648 (7.1%) had a MI, 389 (4.3%) had an ischemic stroke, and 587 (6.4%) were hospitalized with congestive heart failure. Of the deaths, only 526 (43.0%) were classified as cardiovascular deaths. In addition, 326 (3.6%) patients were hospitalized with a bleeding event.

Associations Between Treatments and Outcomes in the Stratified PS-Matched Population

Clinical characteristics between those with and without treatment were well balanced in the 4 PS strata ([online-only Data Supplement Tables III through VI](#)). The association of the different treatments and MACE and the individual components of MACE, respectively, are shown in Table 2 and [online-only Data Supplement Figure II](#). The risk of experiencing a MACE was 18% lower (HR, 0.82; 95% CI, 0.73–0.93) in patients with ACEI/ARB in comparison with no ACEI/ARB; and 23% lower (HR, 0.77; 95% CI, 0.68–0.87) in patients with statins in comparison with no statins. In patients on β -blockers in comparison with patients not using β -blockers, there was a 14% reduction in MACE (HR, 0.86; 95% CI, 0.74–1.01). For patients on DAPT in comparison with without DAPT, there was a nonsignificant 10% lower risk of MACE (HR, 0.90; 95% CI, 0.74–1.08) during the first year after discharge and a nonsignificant 33% higher risk of hospitalization for a bleeding event (HR, 1.33; 95% CI, 0.73–2.42).

Table 1. Baseline Characteristics, Medications at Admission, and Medication at Discharge

Total, n	9136
Demographics	
Age, y (\pm SD)	65.3 \pm 11.4
Female, %	61.0
Medical history, %	
Hypertension	57.6
Diabetes mellitus	16.5
History of CHF	6.6
History of AMI	7.6
History of stroke	7.0
History of bleeding	6.7
History of cancer	1.8
Dementia	0.2
COPD	8.0
Peripheral vascular disease	1.8
Atrial fibrillation	11.1
Current smoking	20.0
ECG changes on admission, %	
ST-segment elevation	17.1
Laboratory values on admission	
Creatinine, μ mol/L (\pm SD)	80.7 \pm 39.8
LDL cholesterol, mmol/L (\pm SD)	3.1 \pm 1.0
Medications on admission, %	
Aspirin	22.9
Other antiplatelets	3.6
Warfarin	5.1
β -Blockers	27.4
ACE -inhibitors	16.5
ARB	12.0
Statins	19.0
Medications at discharge, %	
Aspirin	90.1
Other antiplatelets	69.7
Warfarin	8.9
β -Blockers	83.4
ACE inhibitors	49.5
ARB	13.7
Statins	84.5

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; and LDL, low-density lipoprotein.

The associations between the different treatments and MACE were consistent across subgroups based on sex and age, with the exception of a significant interaction ($P=0.002$) between ACEI/ARB treatment and age (Table 3).

Kaplan-Meier curves of survival free of MACE in the 1:1 PS-matched populations are shown for the 4 treatments in Figure 2.

Sensitivity Analysis

We performed a number of sensitivity analyses. First, analyses of the association between treatment and MACE in PS-matched 1:1 pairs gave similar point estimates for the HRs as in the main analyses (online-only Data Supplement Table VII). Second, we did a separate analysis of the association between ACEI/ARB and MACE in the patients with available data on left ventricular ejection fraction ($n=4684$). The inclusion of left ventricular ejection fraction in the Cox proportional hazards model lowered the HR somewhat in comparison with the model without the left ventricular ejection fraction (HR, 0.75; 95% CI, 0.64–0.88 versus HR, 0.82; 95% CI, 0.73–0.93). Third, as expected, there was no significant association between treatment and bleeding complications with HRs close to 1 in those treatments not expected to influence bleeding: statins (HR, 0.99; 95% CI, 0.70–1.39), ACEI/ARB (HR, 1.04; 95% CI, 0.75–1.43), and β -blockers (HR, 0.92; 95% CI, 0.63–1.35) (Table 2).

DISCUSSION

The present study is the first study to evaluate the association between commonly used secondary prevention treatments and long-term outcome in a large cohort of unselected patients with MINOCA. Among 9136 consecutive MINOCA patients admitted to a cardiac unit in Sweden between 2003 and 2013 and followed for a mean of 4.1 years we can report a significantly 23% and 18% lower adjusted risk of MACE in patients treated with statins and ACEI/ARB, respectively. For treatment with β -blockers, there was a 14% reduction in MACE, not reaching statistical significance. In contrast, DAPT treatment was not associated with a significantly lower risk of MACE during 1-year follow-up.

MI With Nonobstructive Coronary Arteries

With the widespread use of coronary angiography in the management of acute MI there has been an increasing awareness that a proportion of MI patients have no evidence of significant obstructions of the coronary arteries. A systematic review of the literature⁴ estimated the prevalence of MINOCA to be 6% among patients diagnosed with MI, which is close to the prevalence of 8.0% in the present SWEDEHEART registry cohort.

Although patients with MINOCA seem to have a better short- and long-term prognosis than patients with

Table 2. Outcomes

	Statins n=7512	ACEI/ARB n=5904	β -Blockers n=6362	DAPT* n=8118
MACE	0.77 (0.68–0.87)	0.82 (0.73–0.93)	0.86 (0.74–1.01)	0.90 (0.74–1.08)
All-cause mortality	0.66 (0.57–0.77)	0.87 (0.74–1.02)	0.81 (0.66–0.99)	0.75 (0.56–1.01)
CV mortality	0.59 (0.47–0.75)	0.91 (0.70–1.18)	0.80 (0.57–1.14)	0.87 (0.54–1.40)
AMI	0.88 (0.68–1.13)	0.83 (0.67–1.03)	0.74 (0.56–0.97)	1.02 (0.71–1.47)
Stroke	0.67 (0.50–0.90)	0.80 (0.60–1.06)	0.97 (0.66–1.41)	0.82 (0.52–1.30)
CHF	0.88 (0.70–1.12)	0.92 (0.70–1.21)	0.88 (0.62–1.23)	0.83 (0.58–1.17)
Bleeding events	0.99 (0.70–1.39)	1.04 (0.75–1.43)	0.92 (0.63–1.35)	1.33 (0.73–2.42)

The associations, HR (95% CI), between treatments and outcomes. Pooled propensity score stratified analysis. ACEI indicates angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; DAPT, dual antiplatelet therapy; HR, hazard ratio; and MACE, major adverse cardiac events.

*Follow-up for DAPT 1 year postdischarge.

MI with significant CAD,⁴ the rate of long-term serious cardiovascular events is not trivial, especially considering that MINOCA patients are younger and have fewer comorbidities.^{3,4,10} The 4-year mortality of $\approx 13\%$ in the present study is in line with the 3.5% 1-year mortality found in the systematic review by Pasupathy et al⁴ and the 3.3% 1-year mortality in a French registry study.¹¹ The lower use of long-term secondary prevention treatments in the MINOCA patients in the present SWEDEHEART cohort is also consistent with what previously has been described.¹⁰ Given this consistency with data from the literature and the large unselected population from a whole nation, the present study cohort seems representative for the general MINOCA population.

Association Between Treatments and Outcome

The association between treatment with statins and outcome in the present study is in line with the consistent results of statin treatment in secondary and in primary prevention randomized controlled trials (RCTs), as well.¹² The effect size on MACE in the present study are also comparable to the effect size seen in these RCTs.¹² Probable mechanisms explaining the effect of statins are slowing of the progress of atherosclerotic lesions and stabilizing of plaques, especially in those MINOCA patients with minor,

nonsignificant CAD, because plaque ruptures causing MI may also occur from nonsignificant plaques.¹³ In addition, the protective effects on endothelial function¹⁴ may be a possible mechanism of the positive effects in MINOCA patients. There is strong evidence for the use of renin-angiotensin system blockers (ACEI/ARB) in patients with MI and heart failure and depressed left ventricular function.^{15–17} Also, in patients with CAD and absence of heart failure or depressed left ventricular function, ACEI treatment has shown beneficial effects on mortality, and morbidity, as well, in a meta-analysis of RCTs.¹⁸ Suggested mechanisms for the positive effects in the latter group are blood pressure-lowering effect, sympathoinhibitory effects, effects on the endothelial function, and antifibrotic effects on the myocardium,^{17,19} all of which may also be of relevance in MINOCA patients and may explain the association between ACEI/ARB treatment in the present study.

There is experimental evidence that increased sympathetic activation is of importance for the occurrence of cardiovascular events, and therefore β -blocker treatment after MI would be beneficial.¹⁹ However, there is a lack of contemporary RCTs evaluating β -blocker treatment in MI patients, and in MINOCA patients, as well. International guidelines differ in their recommendations about the use of β -blockers after acute MI; American guidelines recommend routine treatment with β -blockers,²⁰ whereas Euro-

Table 3. Subgroups

	Statins	ACEI/ARB	β -Blockers	DAPT*
Women	0.80 (0.69–0.94) n=4550	0.75 (0.64–0.88) n=3557	0.89 (0.73–1.08) n=3817	0.86 (0.68–1.09) n=4995
Men	0.70 (0.57–0.85) n=2967	0.95 (0.78–1.16) n=2347	0.82 (0.64–1.06) n=2545	0.92 (0.68–1.25) n=3123
<70 y	0.73 (0.60–0.90) n=4718	0.96 (0.80–1.15)† n=3861	0.88 (0.70–1.10) n=4192	0.83 (0.60–1.13) n=5066
≥ 70 y	0.85 (0.72–0.99) n=2799	0.74 (0.63–0.87)† n=2043	0.83 (0.68–1.03) n=2170	0.96 (0.76–1.21) n=3052

The associations, HR (95% CI) between treatments and MACE in relation to sex and age. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DAPT, dual antiplatelet therapy; and HR, hazard ratio.

*Follow-up for DAPT 1 year postdischarge.

†Statistically significant interaction between age and ACEI/ARB ($P=0.002$).

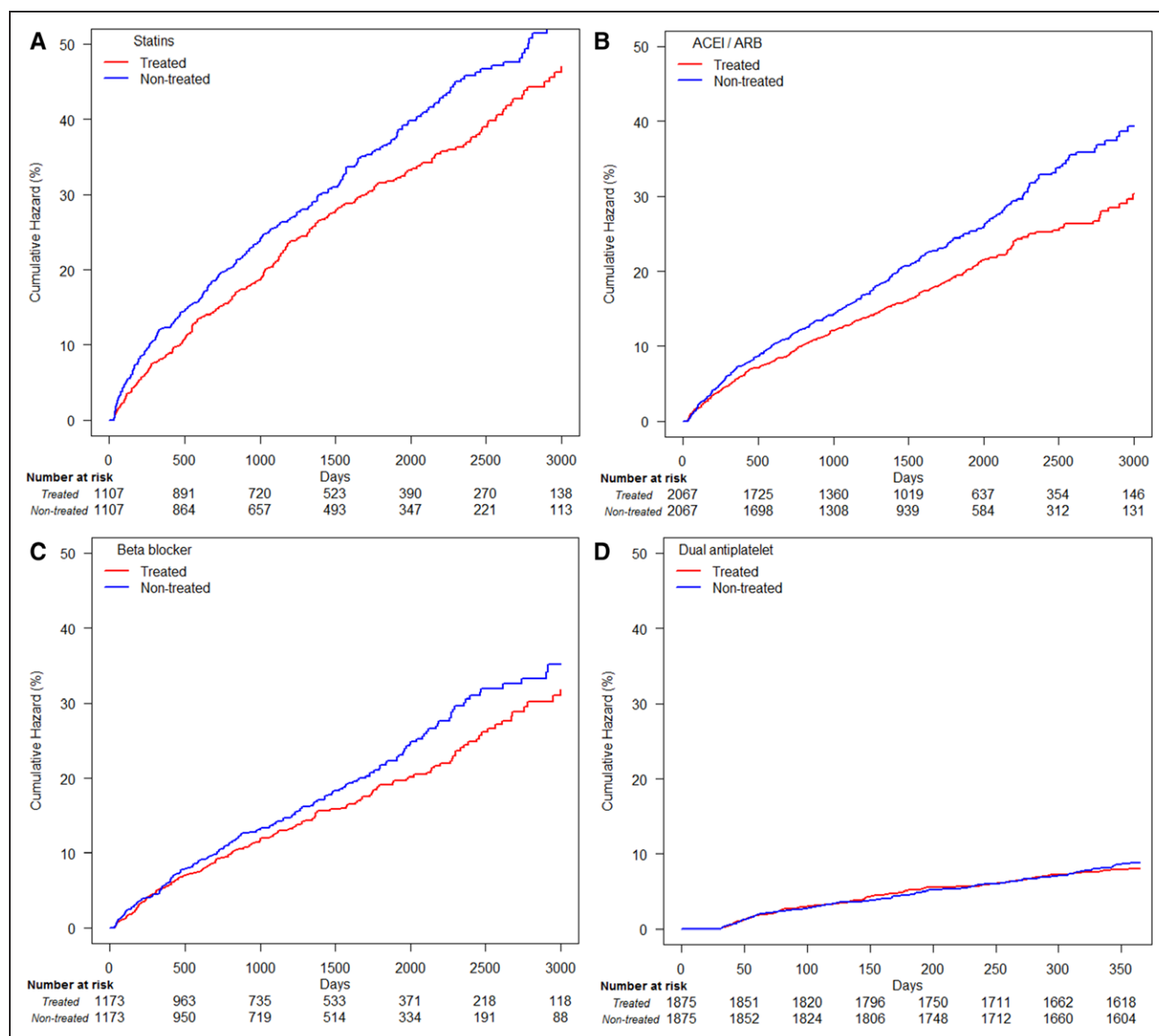


Figure 2. Survival curves for treated and untreated in the 1:1 propensity score-matched populations.

A, Statins. **B**, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). **C**, β -blockers. **D**, Dual antiplatelet treatment.

pean guidelines restrict the recommendation to patients with heart failure or left ventricular systolic dysfunction.²¹ In MINOCA patients, some authorities recommend treatment with β -blockers, mostly based on theoretical considerations.²² Observational studies in post-MI patients and in patients with Takotsubo cardiomyopathy have failed to show long-term beneficial effects of β -blocker treatment on cardiovascular events.^{23–25} Also, in the present study of MINOCA patients, we were not able to show a significantly reduced occurrence of MACE in patients on β -blockers. However, β -blocker treatment, unlike the 3 other studied treatments, was associated with a significantly decreased adjusted risk for MI (Table 2).

DAPT decreases the risk of cardiac events after acute MI^{26,27} and is recommended for up to a year in current

guidelines.²¹ During the time of the present study, DAPT in Sweden consisted almost exclusively of a combination of aspirin 75 mg once daily and clopidogrel 75 mg once daily, and the recommended length of treatment after acute MI varied greatly from 3 months up to a maximum of 1 year at different hospitals. It is rather unlikely that DAPT would have lasting effects after the patient has stopped taking the treatment. Hence, we chose a 1-year follow-up period for the evaluation of DAPT treatment. We could not show a significant association between DAPT and MACE, and in the 1:1 propensity-matched population the survival curves in the Kaplan-Meier analysis were superimposed during the 1-year follow-up. There was no significant association with new MIs, which should be the primary effect of DAPT.²⁶ However, there was not a significantly higher risk of bleed-

ing events during follow-up. Taken together, our findings question the hypothesis that transient thrombus formation overlying a plaque rupture or erosion is a common cause of MINOCA. However, our findings must be interpreted cautiously, because the CI was rather wide and the exact duration of DAPT in the individual patient is not known.

Limitations

A number of inherent limitations in observational studies also apply to this study. First, residual confounding can never be fully excluded. However, we have used PS matching to minimize the risk of residual confounding and have performed several sensitivity analyses indicating that the PS matching was successful in making the groups with and without respective treatment comparable. Nevertheless, our findings should be verified in randomized clinical trials. Second, in a quality registry like SWEDEHEART there will always be some missing data and the quality of data are not as high as in a properly monitored RCT. However, the rates of missing data on key variables in the present study were low and the accuracy of the data in SWEDEHEART has been found to be high.⁶ Because of the unique Swedish personal identification number and the mandatory health registries managed by the National Board of Health and Welfare we had complete follow-up in all patients. In Sweden, the diagnoses of MI, stroke, and heart failure have all been shown to have high validity.^{28–30} Third, the data available in SWEDEHEART do not permit separation of the patients into those without any signs of atherosclerotic lesions and those with signs of atherosclerotic lesions but no stenosis of $\geq 50\%$ on the coronary angiogram. Studies have indicated that these subgroups constitute $\approx 50\%$ each of the MINOCA population.³ Furthermore, because all coronary angiographies were performed in clinical routine and the evaluations of the angiograms were done locally at each hospital, there might be a proportion of the patients in the present study that would have been deemed to have significant stenosis and thus not MINOCA or vice versa, if all angiograms had been evaluated at a core laboratory. Fourth, we only counted events occurring ≥ 30 days after discharge, and there were 2 reasons for that: During the first 30 days it is not possible to separate a new MI from a second hospitalization for the index MI in the National Patient Register; and it is also unlikely that the evaluated treatments have large immediate protective effects (except for DAPT) and that events occurring the first few weeks more closely reflect the seriousness of the index infarct. Fifth, we lack information on the long-term adherence to the discharge medications in the present study. However, data from the secondary prevention part of the SWEDEHEART registry indicate that the adherence to secondary prevention treatment the first year after MI in Sweden is high.³¹ Sixth, MINOCA patients constitute a heterogeneous group. We have no information in the registry on whether further examinations were performed after the hospitaliza-

tion, eg, MRI looking for evidence of myocarditis that was not recognized clinically. In studies of MINOCA patients evaluated with late-enhancement MRI, approximately one-third had signs of myocarditis.⁴ Ideally, it would have been preferable to be able to exclude patients with MRI-proven myocarditis. There might also be some cases of Takotsubo cardiomyopathy in the cohort, especially during the first years of the study period where the awareness of the diagnosis of Takotsubo was limited. Nevertheless, from a pragmatic point of view, we think the study population is appropriate, because these are the patients the clinicians meet in clinical routine and for whom they have to make decisions regarding secondary prevention treatments.

CONCLUSIONS

The results of this large observational study in patients with MINOCA indicate long-term beneficial effects on outcome of treatment with statins and ACEI/ARBs and possibly of β -blockers, but no benefit of DAPT. Despite the careful statistical methodology, some residual confounding cannot be excluded. Therefore, properly designed and powered randomized clinical trials to confirm these results are warranted.

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DISCLOSURES

Drs Lindahl, Baron, Erlinge, Hadziosmanovic, Nordenskjöld, and Gard have no conflict of interests in relation to the present study. Dr Jernberg received modest lecture and consultancy/advisory board fees from AstraZeneca, Aspen, Amgen, and MSD.

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FOOTNOTES

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Medical Therapy for Secondary Prevention and Long-Term Outcome in Patients With Myocardial Infarction With Nonobstructive Coronary Artery Disease

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SUPPLEMENTAL MATERIAL

Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with non-obstructive coronary artery (MINOCA) disease

B Lindahl et al.

<i>Item</i>	<i>Description</i>
Supplemental Statistical methods	
Supplemental Table 1.	Endpoint definitions by ICD-10 codes.
Supplemental Table 2.	List of covariates
Supplemental Table 3.	Baseline characteristics and medications at admission in the propensity score (PS) matched population in relation to statin treatment
Supplemental Table 4.	Baseline characteristics and medications at admission in the propensity score matched population in relation to ACE inhibitor/ARB treatment
Supplemental Table 5.	Baseline characteristics and medications at admission in the propensity score matched population in relation to beta-blocker treatment
Supplemental Table 6.	Baseline characteristics and medications at admission in the propensity score matched population in relation to dual antiplatelet treatment
Supplemental Table 7.	Matched pair analysis
Supplemental Figure 1. A-D	Distribution of propensity scores in patients with and without treatment.
Supplemental Figure 2. A-D	Forest plots showing the hazard ratios for treated versus non-treated regarding major adverse cardiac outcomes (MACE)
Supplemental References	

Supplemental Statistical methods

Imputation (MI)

Multiple imputation of missing values of smoking, plasma creatinine and treatment at admission with ACEI or ARB was performed (using the SAS function PROC MI and arbitrary missing pattern) with all variables in the covariate section used to produce the values for imputation. We used five imputed datasets to ensure that our effect estimates were not overly inaccurate due to Monte Carlo variability.¹ The results for each imputation were combined (using SAS function PROC MIANALYZE).

Propensity score estimation

An initial propensity score (PS) model was estimated using those variables that were considered to affect treatment selection. A causal structure of a set of variables was used in the PS model. To estimate the propensity score, a logistic regression model was used in which treatment status was regressed on relevant covariates (Supplemental Table 2).

Distribution of PS, treated vs non-treated

PS probabilities for treated vs non-treated patients were presented in a histogram as a way to check whether or not there were some patient characteristics (covariate patterns) that defined groups of patients in whom there were no variability in treatments.

PSs allow us to limit model extrapolation by excluding patient groups from the analysis in whom no treatment effect can be estimated because almost all patients were either never or always treated.

Trimming outer regions of PS

Non-overlap outer regions of PS were therefore excluded (trimmed) from the analyses. (Supplemental Figure 1 A-D) and then four equal-size stratas were formed, using the quartiles of the estimated propensity scores.

Balance Diagnostics

To assess whether the propensity score model has been adequately specified, balance diagnostics for comparing the distribution of covariates between treated and non-treated groups in each propensity-score strata was performed (Supplemental Table 3)

PS stratified

Within each stratum^{2,3}, the association between treatment and outcome was estimated by comparing directly between treated and untreated subjects using cox proportional hazards models with adjustment for discharge medications. The stratum-specific estimates of hazard ratios (HRs) were pooled across stratum to estimate an overall association; pooled HRs were calculated using fixed-effects model⁴. Results were presented as Hazard Ratios (HR) and 95 % confidence intervals (CI) by strata and in total. Pooled HRs were calculated in the total study population and in subgroups based on age and gender

PS 1:1 matching

In addition we also estimated the associations between the different treatments and outcome using 1:1 propensity score matching. We used the imputed dataset for the purpose of matching. In order to determine referent subjects for each index, the dataset was searched for the one nearest neighbor, non-replaced match⁵. A 1:1 nearest neighbor matching algorithm was used, described by Rosenbaum et al.⁶. For every patient in the non-treated group, one best-matched patient in the treated group was selected using a matching algorithm⁷, such that the difference in propensity scores between the matched subjects was as low as possible, but differed by at most 0.01 (the caliper width). If no suitable match within the 0.01 caliper was found in the treated group, the untreated patient was excluded from the matched data set. The same procedure was performed by each imputed dataset. The association between treatment and outcome was analyzed using multivariable Cox proportional hazards regression with shared frailty to account for matched pairs. Adjustment was made for discharge medications. The

results for each imputation were combined (using SAS function PROC MIANALYZE and were presented as HRs and 95 % confidence intervals (CI).

The underlying proportional hazards assumptions of the Cox Proportional Hazard models were verified by Schoenfeld residual tests.

We also used the 1:1 matched populations for producing survival curves regarding MACE for treated and non-treated patients using the Kaplan-Meier method.

All analyses were performed using SAS Software Version 9.4 (SAS Institute, Cary, NC, USA) and R (version 3.2.2).

Supplemental Table 1. Endpoint definitions by ICD-10 codes.

Endpoint	ICD-10 code
Cardiac death	I00 - I78
Myocardial infarction	I21, I22, I23
Ischemic stroke	I63, I64
Heart failure	I50, K761, I971, I110
Major Bleeding	I60, I61, I62, I850, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, N02, R310, R311, R318, R040, R041, R042, R048, R049, R58, T810, I983, D629, DR029

Supplemental Table 2. List of covariates.

Complete dataset without imputation: N=7874 patients

Dataset multiple imputation: N=9011 patients

Variable	Missing data (n)
County of residence	0
Year of admission	0
Age	0
Gender	0
Smoking (ongoing, previous, never)	491*
Diabetes	0
Hypertension	0
Heart failure	0
Previous myocardial infarction	0
Previous stroke	0
Atrial fibrillation	0
Peripheral vascular disease	0
Cancer	0
Chronic obstructive pulmonary disease	0
Dementia	0
Previous hospitalization for bleeding (major/minor)	0
Plasma Creatinine at admission	422*
Warfarin treatment at admission	41
Aspirin at admission	41
Dual antiplatelet treatment at admission	48
Statins treatment at admission	35
ACE-inhibitor or Angiotensin Receptor Blocker treatment at admission	468*
Beta-blocker treatment at admission	43
Diuretic treatment at admission	41
Intravenous diuretic treatment during hospitalization	33
Warfarin treatment at discharge	47

*imputation performed

Supplemental Table 3. Baseline characteristics and medications at admission in the propensity score (PS) matched population in relation to statin treatment

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
N=	7697	1413			6169	1348	
Demographics							
Age, y (±SD)	65.2 ± 11.0	66.0 ± 13.4	0.0228				
				1	68.6 ± 10.3	68.9 ± 12.8	0.5793
				2	64.2 ± 11.5	64.7 ± 13.8	0.4841
				3	62.9 ± 11.2	62.2 ± 13.4	0.3725
				4	63.1 ± 11.0	63.6 ± 13.0	0.5963
Female, %	60.1	65.5	0.0001				
				1	73.7	72.6	0.6252
				2	67.7	68.2	0.8541
				3	61.4	63.4	0.5287
				4	39.5	36.8	0.4998
Medical history, %							
Hypertension	58.2	54.3	0.0062				
				1	56.9	56.4	0.8497
				2	49.6	51.3	0.5685
				3	46.0	48.2	0.4948
				4	60.0	56.4	0.3808
Diabetes	17.2	12.6	<.0001				
				1	12.7	10.9	0.2864
				2	10.5	12.5	0.2686
				3	8.6	9.3	0.6820
				4	20.1	20.9	0.8187
History of congestive heart failure	21.3	32.1	<.0001				
				1	50.9	57.3	0.0098
				2	18.2	18.4	0.9297
				3	6.8	7.4	0.7169
				4	11.4	8.6	0.2725
History of acute myocardial infarction	7.7	7.1	0.5101				
				1	9.4	10.1	0.6547
				2	3.8	5.0	0.3126
				3	2.8	1.6	0.2554
				4	6.2	5.5	0.7386
History of stroke	6.9	7.3	0.6210				
				1	10.0	9.7	0.8391
				2	4.3	6.1	0.1455
				3	2.7	2.3	0.7275
				4	3.9	3.1	0.5947
History of bleeding	6.3	9.0	0.0002				
				1	12.6	14.5	0.2514
				2	6.6	6.7	0.9652
				3	3.6	1.9	0.1649
				4	3.4	2.5	0.5047
History of cancer	1.7	2.7	0.0090				
				1	4.0	3.9	0.9290
				2	1.6	2.6	0.2105
				3	1.0	1.2	0.7869

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
				4	0.8	0.0	0.2646
Dementia	0.2	0.4	0.1927				
				1	0.3	0.7	0.2480
				2	0.2	0.0	0.4126
				3	0.1	0.0	0.5734
				4	0.0	0.0	1.0000
Chronic obstructive pulmonary disease	7.7	9.5	0.0255				
				1	13.6	12.3	0.4430
				2	7.7	10.8	0.0648
				3	5.5	3.5	0.1728
				4	4.1	6.7	0.1187
Peripheral vascular disease	1.9	1.1	0.0399				
				1	1.0	1.0	0.9664
				2	0.7	0.9	0.7576
				3	0.9	0.4	0.4278
				4	1.9	3.7	0.1322
Atrial fibrillation	17.3	26.1	<.0001				
				1	41.0	44.6	0.1368
				2	16.5	15.7	0.7416
				3	6.3	7.8	0.3870
				4	8.3	9.8	0.4981
Current smoking	19.7	16.1	0.0017				
				1	11.7	10.8	0.5377
				2	17.6	16.9	0.7681
				3	20.5	22.6	0.4377
				4	33.7	34.4	0.8740
ECG-changes on admission, %							
ST-segment elevation	16.7	19.3	0.0174				
				1	19.0	19.9	0.6269
				2	17.0	19.0	0.3762
				3	17.5	16.0	0.5724
				4	18.0	23.3	0.0918
Laboratory values on admission							
Creatinine, μ (\pmSD)	80.4 \pm 38.1	82.5 \pm 48.2	0.0726				
				1	83.7 \pm 33.4	90.7 \pm 60.6	0.0011
				2	78.1 \pm 30.7	75.3 \pm 27.4	0.1251
				3	75.8 \pm 33.7	76.2 \pm 23.7	0.8483
				4	80.6 \pm 40.3	76.7 \pm 21.4	0.2295
LDL cholesterol, mmol/L (\pmSD)	5.2 \pm 1.2	4.7 \pm 1.1	<.0001				
				1	5.3 \pm 1.1	4.5 \pm 1.0	<.0001
				2	5.4 \pm 1.1	4.8 \pm 1.0	<.0001
				3	5.4 \pm 1.1	4.9 \pm 1.1	<.0001
				4	5.3 \pm 1.2	4.7 \pm 1.2	<.0001
Medications on admission, %							
Aspirin	22.7	23.8	0.3586				
				1	33.3	35.0	0.4617
				2	16.7	19.0	0.3241
				3	7.6	10.1	0.1732
				4	11.0	10.4	0.8368
Other antiplatelets	3.6	4.1	0.3658				
				1	4.3	6.3	0.0643
				2	1.0	1.5	0.5075

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Supplemental Table 4. Baseline characteristics and medications at admission in the propensity score matched population in relation to ACE inhibitor/ARB treatment

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
N=	5666	3166			3019	2885	
Demographics							
Age, y (±SD)	66.7 ± 10.7	63.0 ± 12.2	<.0001				
				1	59.8 ± 11.4	58.5 ± 12.3	0.0544
				2	63.2 ± 10.8	61.8 ± 11.6	0.0213
				3	65.6 ± 10.8	65.6 ± 10.7	0.8993
				4	68.3 ± 10.2	70.2 ± 10.3	0.0015
Female, %	60.2	62.3	0.0544				
				1	66.0	70.0	0.1180
				2	64.2	60.3	0.1169
				3	56.2	54.0	0.3922
				4	53.8	57.6	0.1856
Medical history, %							
Hypertension	68.7	38.7	<.0001				
				1	12.8	11.0	0.3083
				2	31.8	28.0	0.1124
				3	57.1	56.3	0.7618
				4	74.6	81.5	0.0042
Diabetes	20.8	9.1	<.0001				
				1	1.9	2.2	0.6985
				2	5.1	5.6	0.6724
				3	11.6	11.0	0.7413
				4	25.4	22.3	0.2165
History of congestive heart failure	29.3	12.5	<.0001				
				1	1.7	2.2	0.5086
				2	4.8	4.2	0.5724
				3	14.6	12.5	0.2524
				4	48.7	41.5	0.0113
History of acute myocardial infarction	8.4	6.1	<.0001				
				1	7.4	6.0	0.3220
				2	3.8	3.6	0.8177
				3	4.6	5.0	0.7060
				4	6.4	7.4	0.4555
History of stroke	8.1	5.2	<.0001				
				1	4.4	4.0	0.7103
				2	3.9	3.7	0.8065
				3	5.2	5.5	0.8166
				4	7.0	8.6	0.2808
History of bleeding	6.7	6.1	0.2621				
				1	5.9	7.2	0.3463
				2	4.9	4.7	0.8253
				3	6.1	4.0	0.0685
				4	5.5	7.0	0.2709
History of cancer	1.9	1.8	0.8968				
				1	2.5	1.8	0.3587

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
				2	0.9	1.8	0.1335
				3	1.8	1.4	0.4983
				4	1.1	0.7	0.4812
Dementia	0.2	0.3	0.2944				
				1	0.2	0.4	0.5572
				2	0.0	0.1	0.3498
				3	0.1	0.0	0.3721
				4	0.2	0.0	0.3539
Chronic obstructive pulmonary disease	8.7	7.4	0.0318				
				1	9.2	5.7	0.0115
				2	6.3	6.5	0.8616
				3	6.3	7.5	0.3779
				4	9.5	11.3	0.2912
Peripheral vascular disease	2.2	1.0	<.0001				
				1	0.8	0.5	0.4323
				2	0.7	0.5	0.5895
				3	1.5	1.4	0.8927
				4	1.5	2.0	0.4197
Atrial fibrillation	21.0	14.6	<.0001				
				1	13.2	10.3	0.0949
				2	9.7	12.3	0.1166
				3	15.8	14.5	0.4936
				4	23.5	25.7	0.3634
Current smoking	18.2	20.9	0.0018				
				1	21.6	25.1	0.1452
				2	21.7	21.2	0.8283
				3	20.9	22.3	0.5158
				4	24.2	20.1	0.0849
ECG-changes on admission, %							
ST-segment elevation	18.4	15.1	<.0001				
				1	22.9	15.9	0.0011
				2	19.1	14.1	0.0097
				3	23.0	12.7	<.0001
				4	21.0	15.3	0.0109
Laboratory values on admission							
Creatinine, μ (\pmSD)	81.6 \pm 39.1	79.0 \pm 42.0	0.0034				
				1	76.1 \pm 25.5	75.2 \pm 24.3	0.4926
				2	79.1 \pm 59.2	77.0 \pm 28.4	0.3749
				3	76.7 \pm 24.8	77.3 \pm 25.6	0.6548
				4	81.0 \pm 39.3	81.5 \pm 42.0	0.8236
LDL cholesterol, mmol/L (\pmSD)	5.1 \pm 1.2	5.2 \pm 1.2	0.0003				
				1	5.2 \pm 1.2	5.2 \pm 1.1	0.9047
				2	5.3 \pm 1.2	5.3 \pm 1.3	0.8985
				3	5.3 \pm 1.2	5.2 \pm 1.2	0.4594
				4	5.1 \pm 1.2	5.1 \pm 1.2	0.5136
Medications on admission, %							
Aspirin	26.1	17.2	<.0001				
				1	15.5	13.3	0.2452
				2	12.8	12.3	0.7807

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
				3	19.7	17.9	0.3754
				4	21.0	25.1	0.0860
Other antiplatelets	3.8	2.6	0.0034				
				1	2.3	2.8	0.5839
				2	2.2	1.4	0.2530
				3	2.4	1.4	0.1458
				4	1.9	3.8	0.0320
Warfarin	5.8	3.8	<.0001				
				1	3.6	4.9	0.2481
				2	2.9	2.4	0.5535
				3	2.2	2.9	0.3823
				4	3.8	3.4	0.7149
Beta-blockers	30.9	21.2	<.0001				
				1	18.9	15.8	0.1352
				2	17.9	17.6	0.9049
				3	22.9	23.4	0.8126
				4	23.2	28.7	0.0266
ACE-inhibitors	25.0	2.3	<.0001				
				1	0.0	0.0	1.0000
				2	0.1	0.0	0.2838
				3	0.1	0.0	0.3721
				4	1.4	0.7	0.2616
Angiotensin receptor blocker	17.7	2.1	<.0001				
				1	0.0	0.0	1.0000
				2	0.3	0.0	0.1290
				3	0.0	0.0	1.0000
				4	1.1	0.9	0.7762
Statins	22.3	13.2	<.0001				
				1	9.7	10.7	0.5415
				2	10.6	10.2	0.7733
				3	13.4	13.5	0.9671
				4	16.1	15.8	0.8974
Diuretics	22.3	13.0	<.0001				
				1	9.9	7.6	0.1393
				2	11.9	10.2	0.2786
				3	14.4	16.7	0.2212
				4	14.8	18.5	0.0747
Medications during hospitalization, %							
Intra venous diuretics	16.5	6.3	<.0001				
				1	1.5	0.4	0.0251
				2	2.9	2.0	0.2760
				3	6.0	4.3	0.1491
				4	27.3	23.7	0.1496
Medications at discharge, %							
Warfarin	10.5	6.4	<.0001				
				1	4.0	4.8	0.4855
				2	3.6	4.2	0.5846
				3	7.4	6.1	0.3239
				4	11.8	10.8	0.5907

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
Year of admission							
Period, year (\pmSD)	5.8 \pm 2.6	5.5 \pm 2.6	<.0001				
				1	4.6 \pm 2.5	4.3 \pm 2.3	0.0510
				2	5.9 \pm 2.5	6.2 \pm 2.5	0.0313
				3	6.1 \pm 2.3	6.2 \pm 2.3	0.9687
				4	6.2 \pm 2.2	6.2 \pm 2.3	0.9446

Supplemental Table 5. Baseline characteristics and medications at admission in the propensity score matched population in relation to beta-blocker treatment

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
N=	7600	1514			5031	1331	
Demographics							
Age, y (±SD)	65.6 ± 11.3	63.8 ± 11.9	<.0001				
				1	62.4 ± 12.1	61.7 ± 12.6	0.3353
				2	62.5 ± 11.7	62.5 ± 11.3	0.9867
				3	64.0 ± 11.0	64.5 ± 12.0	0.4469
				4	66.2 ± 10.9	67.5 ± 10.0	0.1064
Female, %	60.4	64.1	0.0068				
				1	75.0	78.6	0.1179
				2	64.1	64.9	0.7769
				3	54.1	51.6	0.4419
				4	46.2	44.0	0.5459
Medical history, %							
Hypertension	59.9	45.8	<.0001				
				1	29.3	31.3	0.4204
				2	37.2	39.4	0.4708
				3	50.7	48.4	0.4862
				4	70.1	72.0	0.5880
Diabetes	17.0	14.0	0.0044				
				1	11.7	13.1	0.4149
				2	10.2	12.4	0.2534
				3	14.0	12.5	0.5030
				4	17.5	15.9	0.5808
History of congestive heart failure	24.3	16.6	<.0001				
				1	9.1	12.9	0.0210
				2	11.5	10.1	0.4490
				3	16.7	15.7	0.6645
				4	30.4	26.6	0.2652
History of acute myocardial infarction	7.7	6.9	0.2902				
				1	7.3	9.7	0.1044
				2	3.4	4.0	0.5644
				3	2.4	2.5	0.9621
				4	4.6	2.9	0.2750
History of stroke	7.2	5.7	0.0377				
				1	5.4	5.9	0.7040
				2	4.8	6.3	0.2648
				3	4.7	5.3	0.6269
				4	6.3	5.8	0.7840
History of bleeding	6.9	5.8	0.1378				
				1	5.4	4.6	0.5358
				2	4.5	4.3	0.8763
				3	5.4	8.2	0.0741
				4	6.9	8.7	0.3400
History of cancer	1.8	2.0	0.6356				
				1	2.4	2.6	0.7637
				2	1.0	1.7	0.2366
				3	1.4	0.7	0.3658
				4	1.2	1.0	0.7453

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
Dementia	0.2	0.2	0.9232				
				1	0.4	0.0	0.1779
				2	0.1	0.3	0.3355
				3	0.3	0.0	0.3536
				4	0.1	0.5	0.2951
Chronic obstructive pulmonary disease	7.4	11.0	<.0001				
				1	17.5	17.4	0.9378
				2	7.0	7.2	0.9052
				3	3.4	3.9	0.6923
				4	3.2	2.4	0.5520
Peripheral vascular disease	1.9	1.5	0.2535				
				1	1.1	1.6	0.3886
				2	1.0	0.9	0.7613
				3	1.2	1.1	0.8295
				4	2.5	1.9	0.6439
Atrial fibrillation	19.8	13.1	<.0001				
				1	10.2	9.3	0.5637
				2	9.8	9.8	0.9802
				3	11.2	15.3	0.0553
				4	18.7	14.0	0.0999
Current smoking	19.3	18.6	0.5179				
				1	15.8	15.8	0.9832
				2	19.4	17.0	0.3046
				3	22.5	22.4	0.9712
				4	28.3	28.0	0.9229
ECG-changes on admission, %							
ST-segment elevation	17.4	15.5	0.0648				
				1	16.8	12.6	0.0300
				2	20.1	17.8	0.3337
				3	17.3	15.4	0.4306
				4	19.7	15.9	0.1963
Laboratory values on admission							
Creatinine, μ (\pmSD)	81.4 \pm 41.1	77.2 \pm 32.5	0.0003				
				1	73.3 \pm 20.6	71.8 \pm 20.0	0.1707
				2	75.6 \pm 21.0	75.6 \pm 24.0	0.9761
				3	77.8 \pm 22.3	79.7 \pm 28.2	0.2384
				4	83.1 \pm 34.7	83.2 \pm 26.6	0.9673
LDL cholesterol, mmol/L (\pmSD)	5.1 \pm 1.2	5.1 \pm 1.1	0.6957				
				1	5.2 \pm 1.2	5.1 \pm 1.2	0.1316
				2	5.2 \pm 1.1	5.2 \pm 1.1	0.7888
				3	5.2 \pm 1.1	5.2 \pm 1.2	0.7058
				4	5.2 \pm 1.2	5.1 \pm 1.0	0.4070
Medications on admission, %							
Aspirin	23.3	20.8	0.0320				
				1	22.7	26.5	0.1065
				2	12.1	17.5	0.0089
				3	13.1	11.4	0.4280
				4	13.2	9.7	0.1509
Other antiplatelets	3.6	4.0	0.3674				
				1	2.7	4.2	0.1151
				2	1.1	2.6	0.0435
				3	1.5	3.2	0.0424

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
				4	3.9	4.3	0.7604
Warfarin	5.4	3.6	0.0048				
				1	4.3	3.8	0.6744
				2	2.3	2.6	0.7846
				3	1.5	2.5	0.2116
				4	2.5	1.0	0.1635
Beta-blockers	31.3	8.1	<.0001				
				1	0.1	0.2	0.5641
				2	0.2	0.0	0.4539
				3	0.6	0.7	0.8458
				4	6.4	3.9	0.1493
ACE-inhibitors	17.0	13.7	0.0016				
				1	11.6	11.5	0.9618
				2	9.6	13.2	0.0490
				3	13.1	11.8	0.5647
				4	15.9	15.5	0.8691
Angiotensin receptor blocker	12.4	9.8	0.0058				
				1	8.3	9.0	0.6170
				2	7.2	7.6	0.8133
				3	9.9	9.4	0.7974
				4	11.3	15.7	0.0784
Statins	19.5	16.4	0.0059				
				1	16.1	16.2	0.9645
				2	12.4	14.9	0.2096
				3	12.7	11.0	0.4290
				4	13.2	14.0	0.7589
Diuretics	19.1	16.8	0.0433				
				1	18.2	23.6	0.0113
				2	12.5	11.8	0.7299
				3	11.2	10.3	0.6621
				4	10.9	12.1	0.6201
Medications during hospitalization, %							
Intra venous diuretics	13.2	10.5	0.0036				
				1	7.9	8.7	0.5732
				2	9.2	6.9	0.1824
				3	9.8	10.3	0.8099
				4	14.8	13.0	0.5156
Medications at discharge, %							
Warfarin	9.4	6.4	0.0002				
				1	5.8	5.1	0.5703
				2	3.9	5.7	0.1437
				3	4.7	6.4	0.2204
				4	8.2	5.8	0.2365
Year of admission							
Period, year (±SD)	5.5 ± 2.7	5.7 ± 2.8	0.0969				
				1	5.9 ± 3.1	5.9 ± 3.0	0.8470
				2	5.7 ± 2.7	5.8 ± 2.7	0.4997
				3	5.4 ± 2.5	5.6 ± 2.6	0.2738
				4	5.3 ± 2.4	5.2 ± 2.3	0.8790

Supplemental Table 6. Baseline characteristics and medications at admission in the propensity score matched population in relation to dual antiplatelet treatment

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
N=	6036	3060			5838	2280	
Demographics							
Age, y (±SD)	64.6 ± 11.4	66.8 ± 11.4	<.0001				
				1	67.9 ± 10.9	67.6 ± 11.1	0.5389
				2	65.6 ± 11.4	65.5 ± 11.8	0.8271
				3	64.4 ± 11.1	65.2 ± 11.9	0.1319
				4	61.6 ± 11.2	61.9 ± 11.4	0.5789
Female, %	58.6	65.8	<.0001				
				1	80.0	79.1	0.6301
				2	72.0	73.9	0.3760
				3	62.2	61.9	0.9031
				4	31.3	34.7	0.2254
Medical history, %							
Hypertension	56.7	59.3	0.0183				
				1	59.9	58.3	0.4609
				2	56.0	55.7	0.8997
				3	55.1	56.6	0.5785
				4	55.1	58.7	0.2443
Diabetes	16.0	17.4	0.1054				
				1	16.4	18.5	0.2127
				2	15.7	14.5	0.4967
				3	14.4	14.3	0.9770
				4	16.8	16.7	0.9640
History of congestive heart failure	19.1	30.7	<.0001				
				1	37.0	39.4	0.2735
				2	20.6	19.5	0.6040
				3	12.5	14.5	0.2444
				4	9.9	12.6	0.1392
History of acute myocardial infarction	6.8	9.1	<.0001				
				1	11.5	12.8	0.3723
				2	7.1	6.7	0.7542
				3	4.8	5.3	0.6379
				4	4.5	4.4	0.9488
History of stroke	6.6	7.7	0.0519				
				1	5.4	5.2	0.8682
				2	5.4	4.9	0.6544
				3	4.9	4.5	0.7482
				4	8.8	10.1	0.4455
History of bleeding	6.0	8.0	0.0002				
				1	10.7	13.5	0.0564
				2	7.0	6.5	0.6960
				3	4.0	3.9	0.9003
				4	3.2	3.8	0.5605
History of cancer	1.7	2.0	0.3361				
				1	2.7	2.9	0.8253
				2	1.7	1.8	0.8779
				3	1.8	2.0	0.6678
				4	1.0	1.3	0.6640
Dementia	0.2	0.2	0.7675				

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
				1	0.1	0.1	0.8285
				2	0.1	0.5	0.1468
				3	0.1	0.0	0.5736
				4	0.2	0.0	0.3889
Chronic obstructive pulmonary disease	7.3	9.4	0.0004				
				1	13.8	13.1	0.6672
				2	9.5	9.8	0.8280
				3	5.9	6.1	0.8414
Peripheral vascular disease				4	2.3	4.4	0.0281
	1.8	1.8	0.9772				
				1	1.1	1.2	0.9189
				2	1.6	2.0	0.5997
Atrial fibrillation				3	1.9	2.0	0.8858
				4	2.3	1.6	0.4313
	12.3	31.3	<.0001				
				1	29.2	32.4	0.1207
Current smoking				2	14.1	11.4	0.1051
				3	5.6	8.2	0.0420
				4	2.9	4.4	0.1426
	21.3	15.0	<.0001				
ECG-changes on admission, %							
ST-segment elevation	18.2	15.0	0.0002				
				1	20.4	17.5	0.1000
				2	15.9	14.5	0.4231
				3	16.2	15.4	0.6961
Laboratory values on admission				4	19.7	10.8	0.0002
	Creatinine, μ (\pmSD)	79.5 \pm 37.3	82.9 \pm 43.6	0.0001			
				1	85.5 \pm 58.0	85.4 \pm 49.4	0.9516
				2	77.5 \pm 27.8	77.9 \pm 39.1	0.7802
LDL cholesterol, mmol/L (\pmSD)				3	76.7 \pm 31.5	77.7 \pm 26.3	0.5227
				4	79.6 \pm 19.8	81.1 \pm 25.4	0.2167
		5.2 \pm 1.2	5.0 \pm 1.2	<.0001			
				1	5.2 \pm 1.2	5.0 \pm 1.1	0.0042
Medications on admission, %				2	5.2 \pm 1.2	5.2 \pm 1.2	0.9129
				3	5.2 \pm 1.2	5.2 \pm 1.1	0.7164
				4	5.1 \pm 1.2	5.1 \pm 1.5	0.4605
	Aspirin	22.3	23.9	0.0961			
Other antiplatelets				1	28.5	28.5	0.9784
				2	22.9	24.6	0.4027
				3	19.3	20.9	0.4455
				4	19.7	16.7	0.2182
	3.7	3.6	0.8980				
				1	3.9	3.7	0.8740
				2	3.2	4.9	0.0607
				3	2.3	2.5	0.8086
				4	4.7	5.0	0.8086

	Unmatched			PS matched			
	Treated	Non-treated	p-value	PS Strata	Treated	Non-treated	p-value
Warfarin	1.3	12.5	<.0001				
				1	1.4	2.2	0.1522
				2	0.6	0.8	0.6549
				3	0.3	0.4	0.5936
				4	0.3	0.6	0.3445
Beta-blockers	24.3	33.6	<.0001				
				1	33.9	32.1	0.3818
				2	25.1	25.2	0.9340
				3	21.9	21.9	0.9734
				4	17.9	23.0	0.0325
ACE-inhibitors	15.6	18.2	0.0019				
				1	16.0	17.7	0.3265
				2	15.2	13.2	0.2482
				3	14.5	16.0	0.4268
				4	15.9	17.0	0.6283
Angiotensin receptor blocker	11.4	13.1	0.0235				
				1	11.5	10.7	0.5807
				2	11.1	13.2	0.1752
				3	12.2	11.1	0.5206
				4	10.7	9.3	0.4585
Statins	18.7	19.6	0.3008				
				1	14.2	15.1	0.5761
				2	16.3	15.8	0.7719
				3	19.1	17.6	0.4762
				4	22.1	22.4	0.9003
Diuretics	16.7	22.7	<.0001				
				1	25.5	26.5	0.6232
				2	20.5	17.1	0.0771
				3	13.2	16.0	0.1158
				4	10.2	12.6	0.1910
Medications during hospitalization %							
Intra venous diuretics	10.3	17.8	<.0001				
				1	24.4	25.2	0.6788
				2	10.0	12.9	0.0591
				3	6.3	5.5	0.5424
				4	3.8	3.8	0.9923
Medications at discharge, %							
Warfarin	1.4	23.8	<.0001				
				1	0.0	0.0	-
				2	0.0	0.0	-
				3	0.0	0.0	-
				4	0.0	0.0	-
Year of admission							
Period, year (±SD)	5.8 ± 2.6	5.2 ± 2.9	<.0001				
				1	3.5 ± 2.8	3.1 ± 2.8	0.0073
				2	5.8 ± 2.8	5.6 ± 2.8	0.1840
				3	6.7 ± 2.0	6.7 ± 2.0	0.6447
				4	6.5 ± 1.3	6.6 ± 1.3	0.4783

Supplemental Table 7. The associations (HR; 95 % CI) between treatments and MACE. Propensity score matched 1:1 pair analysis. Adjustment for medications at discharge.

	Statins (n=2,694)	ACEI/ARB[†] (n=4,524)	Beta-blockers (n=2,662)	DAPT[‡] (n=4,504)
MACE	0.83 (0.71-0.98)	0.84 (0.73-0.98)	0.83 (0.67-1.03)	1.00 (0.76-1.32)

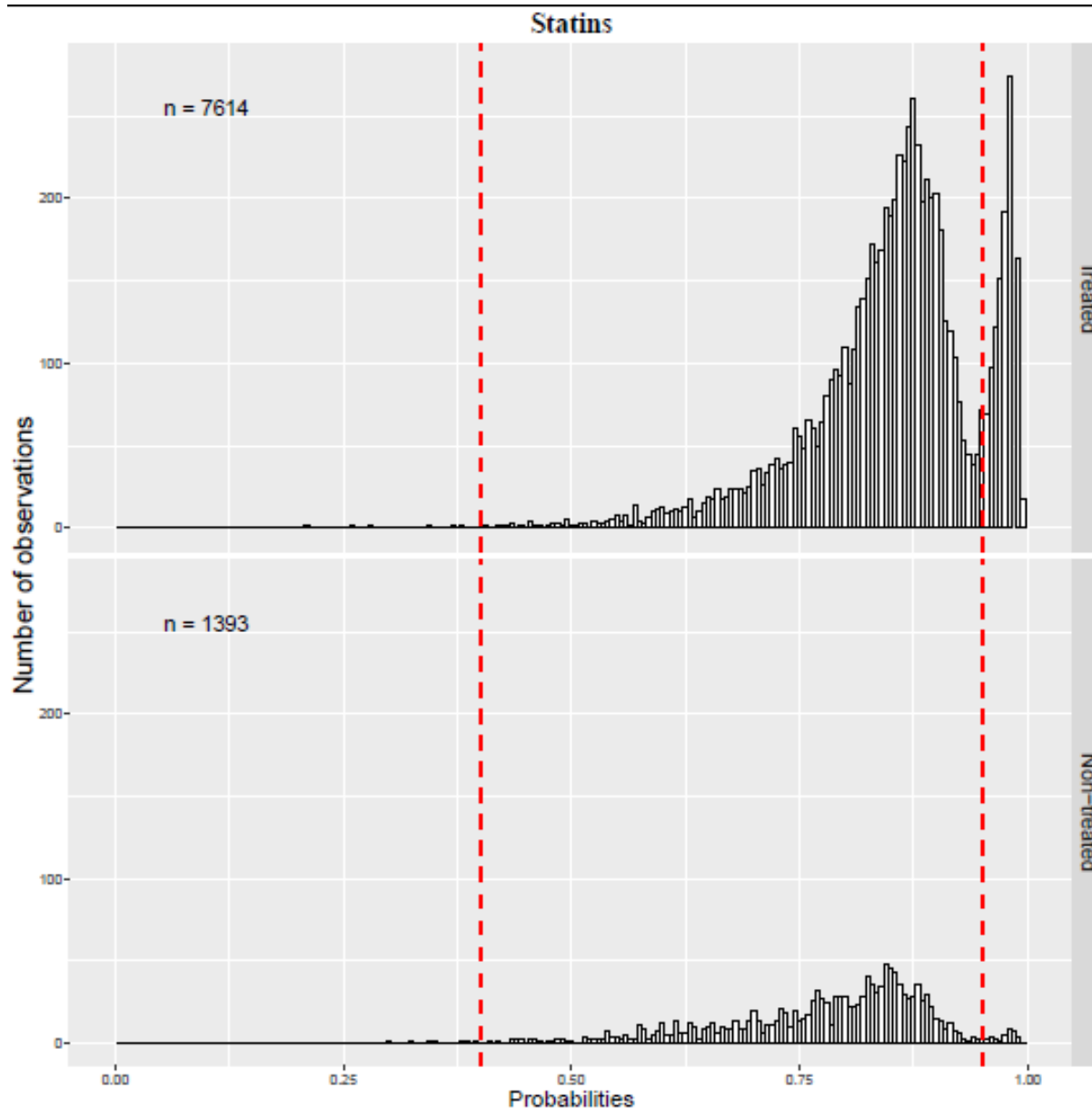
[†]ACE inhibitor

[‡]angiotensin receptor blocker

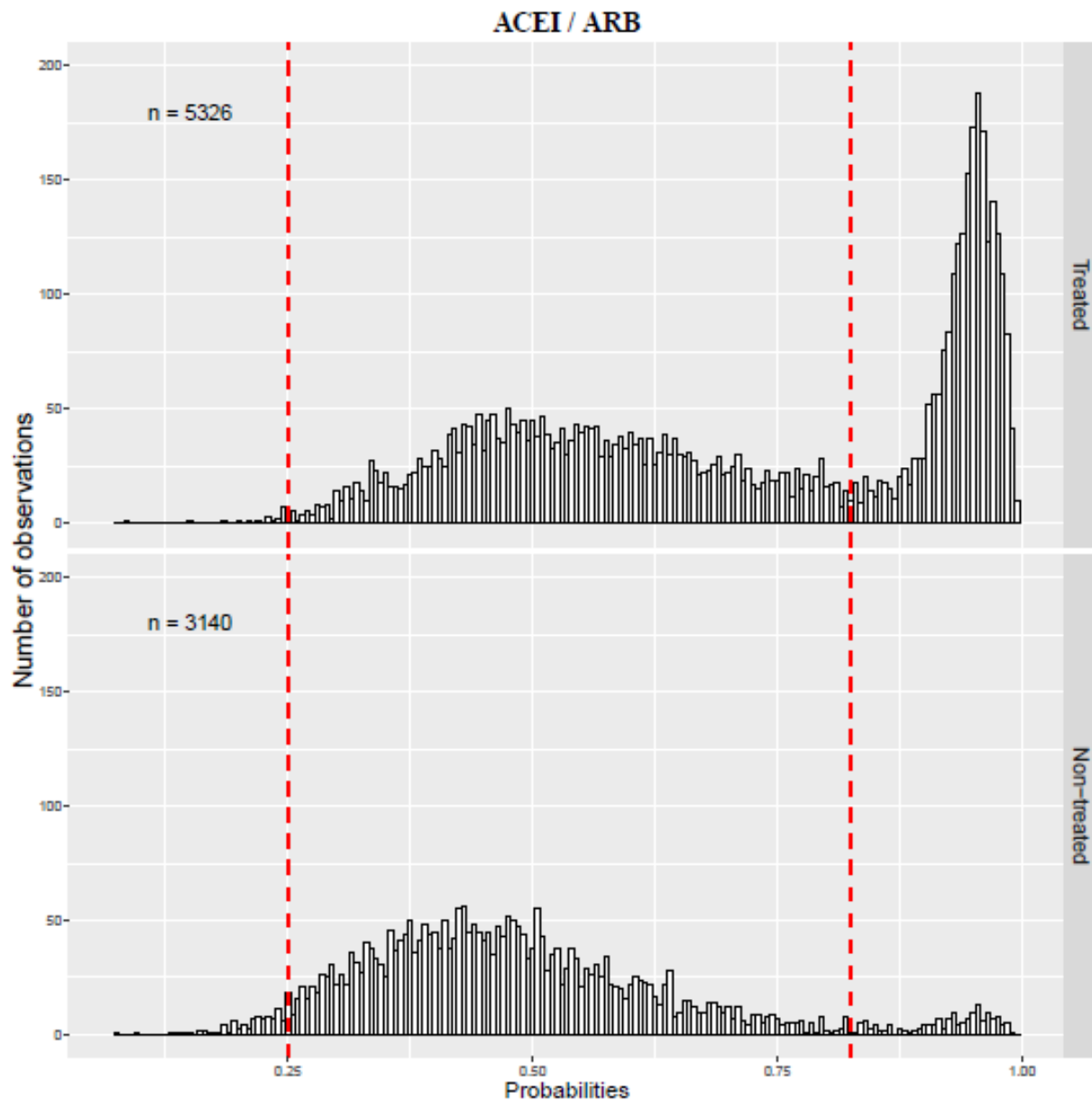
[‡]dual antiplatelet therapy; Follow-up for DAPT one-year post discharge

Supplemental Figure 1. Distribution of propensity scores in patients with and without treatment.

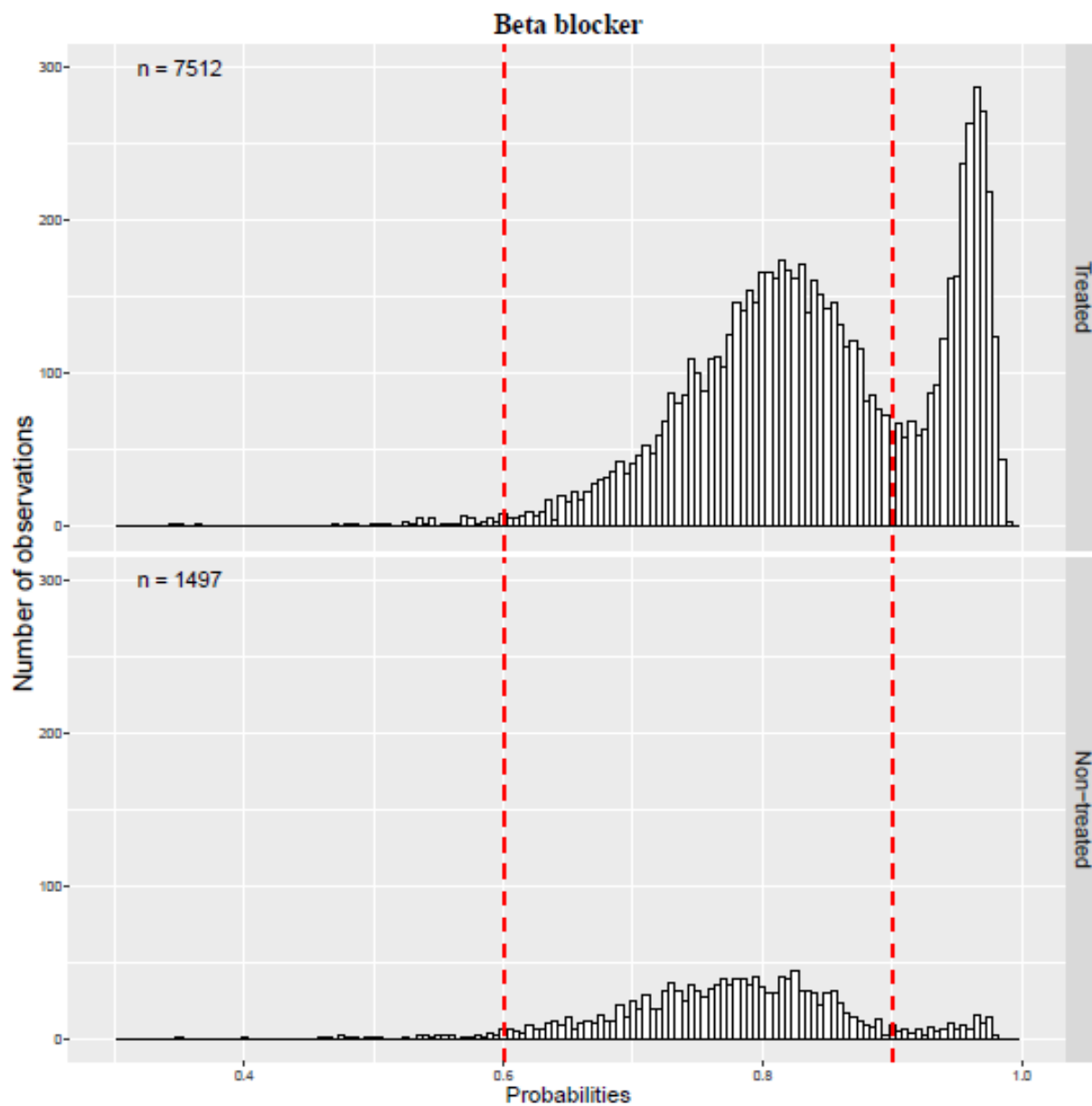
- A. Distribution of propensity scores in patients with and without statin treatment at discharge. Patients with estimated propensity scores to the left of the left broken red line and to the right of the right broken red line were removed from the analysis. Among patients with estimated propensity scores between the two broken red lines, four equal-size stratas were formed, using the quartiles of the estimated propensity scores.



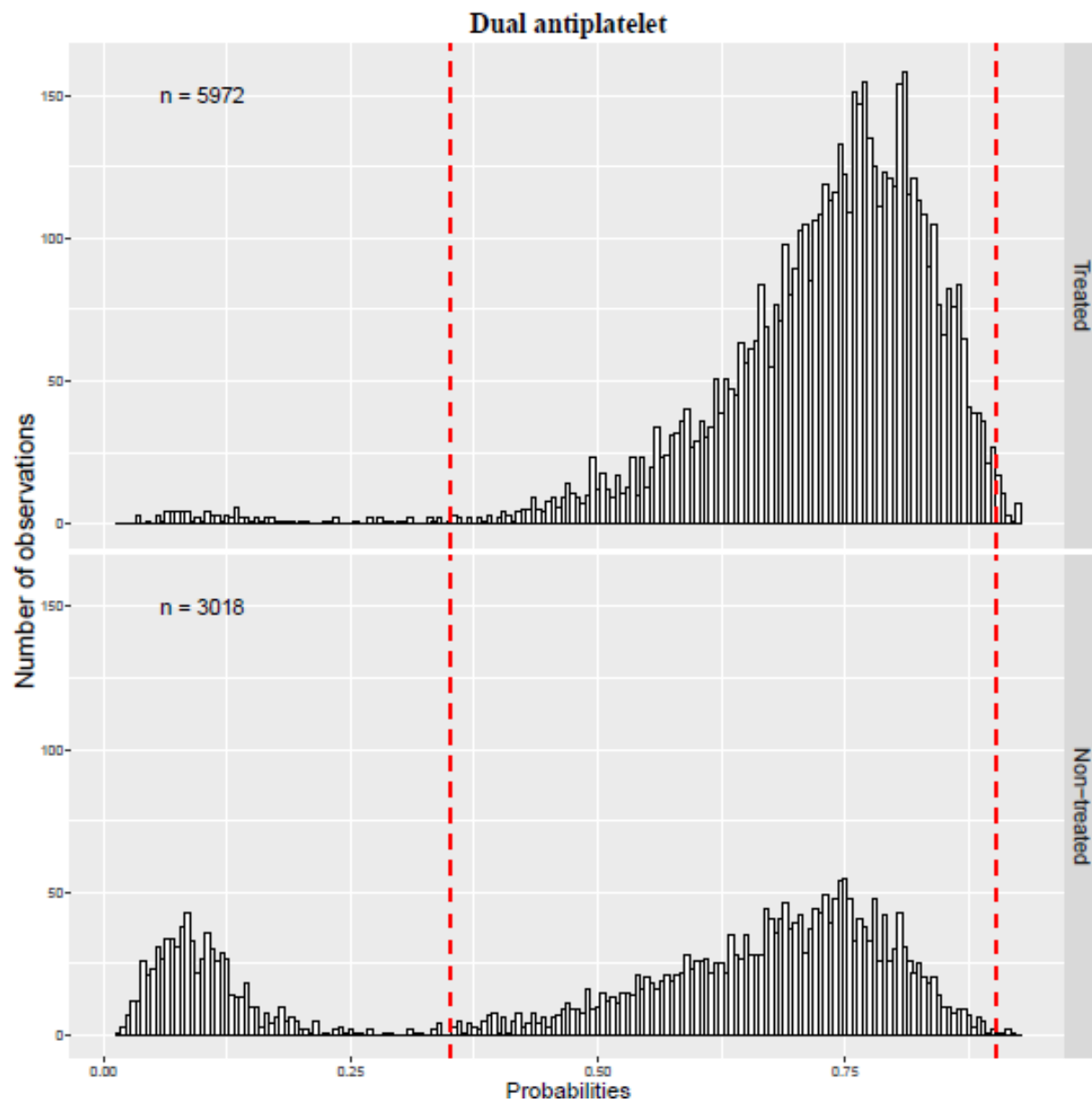
- B. Distribution of propensity scores in patients with and without ACE inhibitor (ACEI)/ angiotensin receptor blocker (ARB) treatment at discharge. Patients with estimated propensity scores to the left of the left broken red line and to the right of the right broken red line were removed from the analysis. Among patients with estimated propensity scores between the two broken red lines, four equal-size stratas were formed, using the quartiles of the estimated propensity scores.



- C. Distribution of propensity scores in patients with and without beta-blocker treatment at discharge. Patients with estimated propensity scores to the left of the left broken red line and to the right of the right broken red line were removed from the analysis. Among patients with estimated propensity scores between the two broken red lines, four equal-size stratas were formed, using the quartiles of the estimated propensity scores.

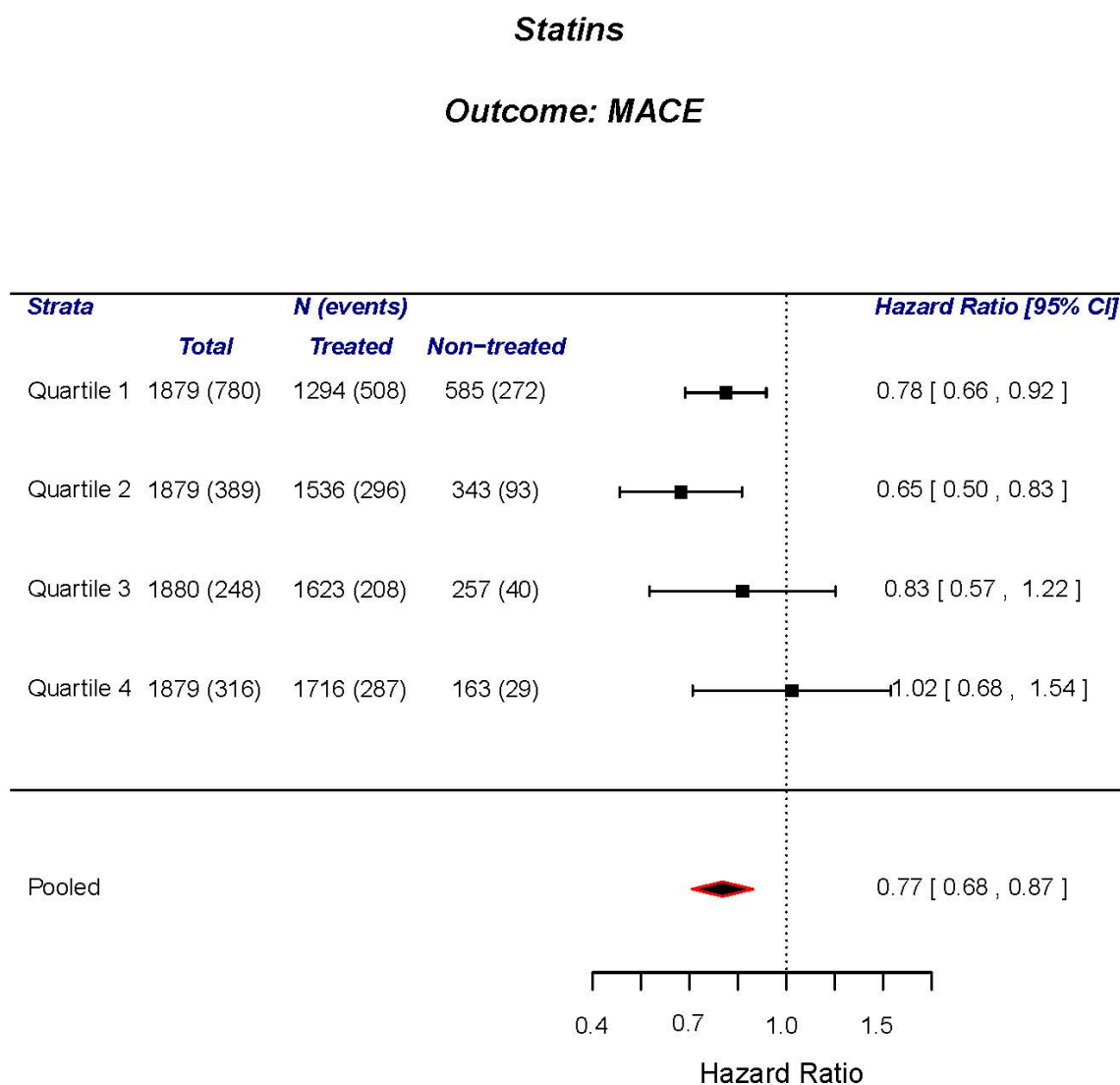


- D. Distribution of propensity scores in patients with and without dual antiplatelet therapy (DAPT) at discharge. Patients with estimated propensity scores to the left of the left broken red line and to the right of the right broken red line were removed from the analysis. Among patients with estimated propensity scores between the two broken red lines, four equal-size stratas were formed, using the quartiles of the estimated propensity scores.

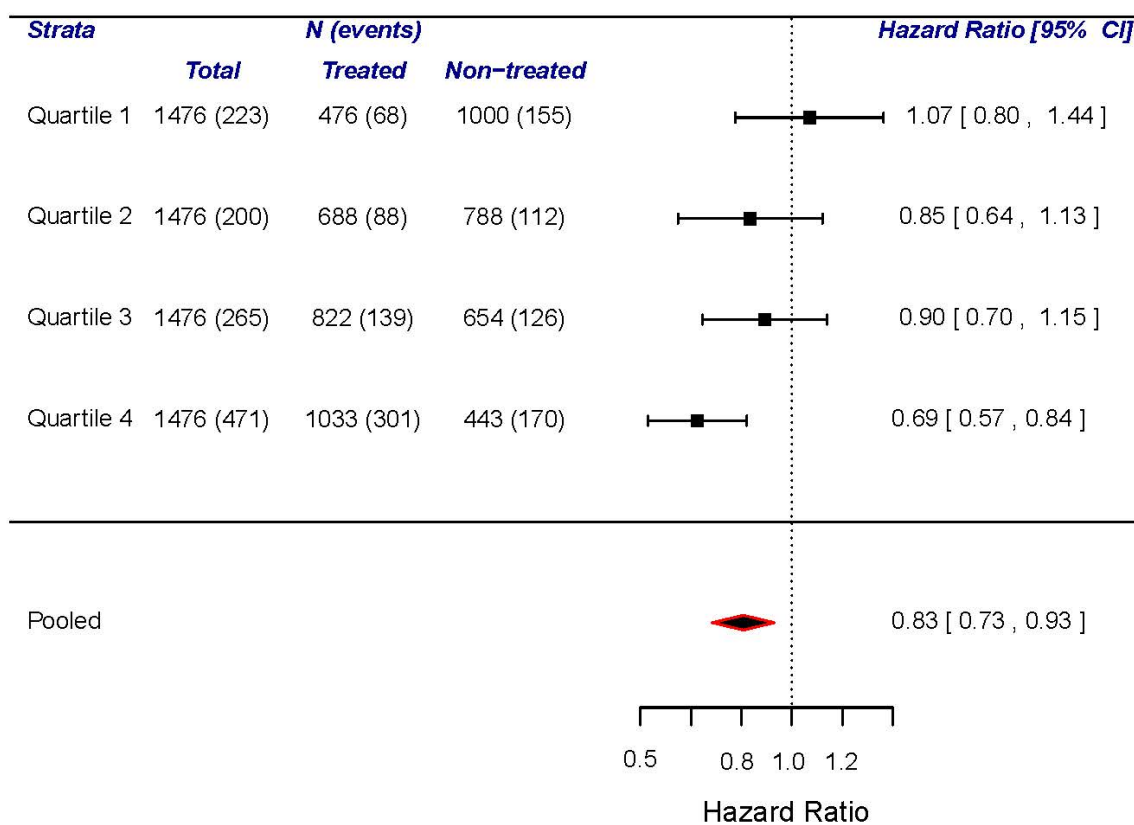


Supplemental Figure 2. Forrest plots showing the hazard ratios for treated versus non-treated regarding major adverse cardiac outcomes (MACE).

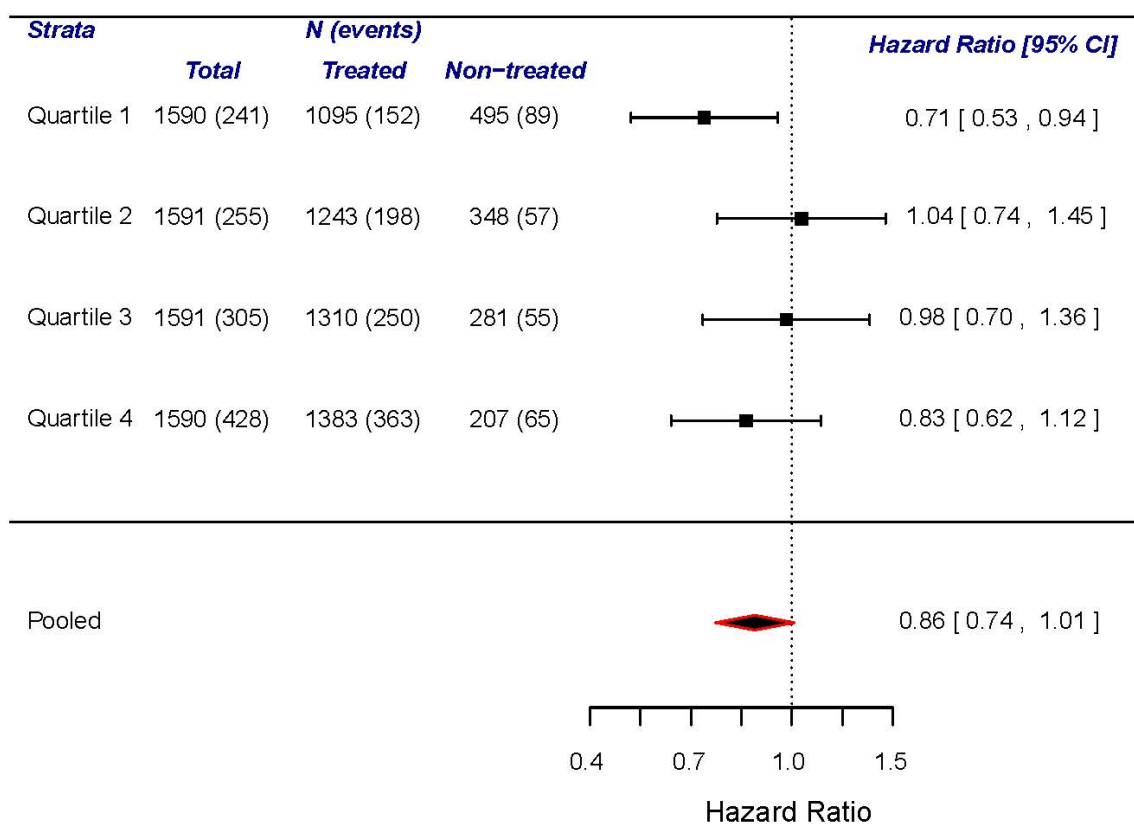
A) Statins



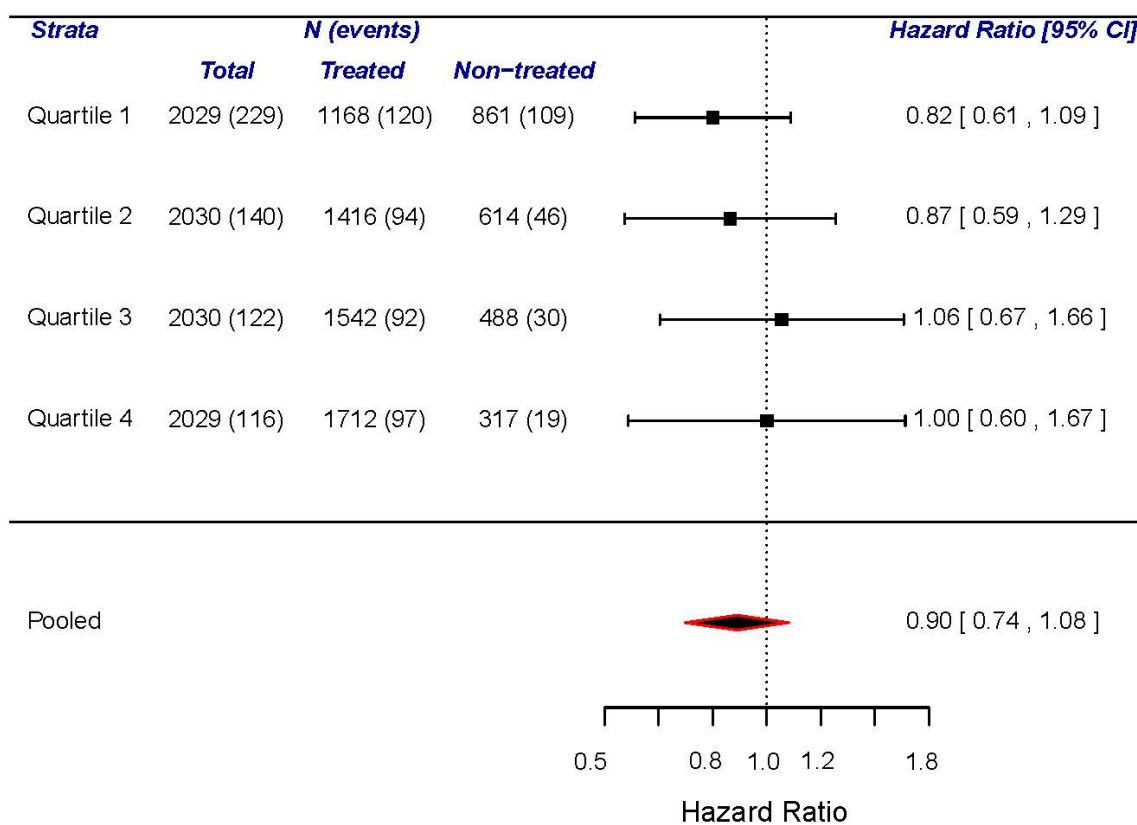
B) ACE-inhibitors (ACEI) or Angiotensin receptor blockers (ARB)

ACEI / ARB**Outcome: MACE**

C) Beta-blockers

Beta blocker**Outcome: MACE**

D) Dual antiplatelet treatment (DAPT)

Dual antiplatelet**Outcome: MACE**

Supplemental References

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Dr Carolyn Lam: Welcome to Circulation On the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Center, and Duke National University of Singapore. Our feature paper this week discusses the very important patient group with myocardial infarction and non-obstructive coronary artery disease, a paper that we will be digging deep into right after these summaries.

The first paper identifies a novel therapeutic target in pulmonary arterial hypertension, and that is nicotinamide phosphoribosyltransferase, a cytozyme which regulates intracellular NAD levels and cellular redox state, regulates histone deacetylases, promotes cell proliferation, and inhibits apoptosis.

This is a paper from first author Dr. Chen and co-corresponding authors Dr. Machado from University of Illinois Chicago and Dr. Garcia from the University of Arizona. The authors found that plasma and mRNA and protein levels of nicotinamide phosphoribosyltransferase were all increased in the lungs and the isolated pulmonary arterial endothelial cells from patients with pulmonary arterial hypertension.

They were also increased in the lungs of rodent models of pulmonary hypertension. Nicotinamide phosphoribosyltransferase deficient mice were protected from hypoxia mediated pulmonary hypertension; whereas, enhanced activity promoted human arterial smooth muscle cell proliferation via paracrine effect and inhibition of activity attenuated pulmonary hypertension in rats.

This paper, therefore, provides evidence that nicotinamide phosphoribosyltransferase plays a role in pulmonary vascular remodeling and its inhibition could be a potential therapeutic target for pulmonary arterial hypertension.

The next study suggests that high sensitivity cardiac troponin T may be an early biochemical signature for clinical and subclinical heart failure. In this study from first author Dr. Seliger, corresponding author Dr. deFilippi, and colleagues from Inova Heart and Vascular Institute, the authors measured high sensitivity cardiac troponin T at baseline among almost five thousand participants in the multi-ethnic study of atherosclerosis MESA cohort, who were initially free of overt cardiovascular disease.

Cardiac magnetic resonance imaging was performed at baseline and repeated 10 years later among 2,831 participants who remain free of interim cardiovascular disease events, among whom 1,723 also received gadolinium enhanced cardiac magnetic resonance for characterization of replacement fibrosis by late gadolinium enhancement. Results showed that a mild elevation of high sensitivity cardiac troponin T identified subjects at highest risk for an increase in left ventricular mass and end diastolic volume over the next 10 years.

Higher levels also associated with an increased incidence of replacement fibrosis, but with no differentiation between ischemic or non-ischemic fibrosis patterns. For the more high levels remained an independent predictor for incident heart failure, coronary heart disease events and cardiovascular events, independent of underlying left ventricular hypertrophy or ejection fraction.

The implications are that myocyte injury, measured with a highly sensitive cardiac specific troponin assay may ultimately be an important early signal used to target therapy to prevent or delay left ventricular remodeling and progression to heart failure.

Does maintenance of cardiovascular risk factors at target eliminate the excess risk of mortality in cardiovascular diseases associated with type 1 diabetes? Well, this question was addressed in the next paper by Dr. Rawshani and colleagues of the Swedish National Diabetes Register in Gothenburg Sweden. The authors compared more than 33,300 patients with type 1 diabetes to more than 166,500 match controls without diabetes from the Swedish National Diabetes Register. They found that patients with type 1 diabetes, with five selected cardiovascular risk factors at target, demonstrated a non-significant excess risk of death compared to controls.

These five risk factors included glycated hemoglobin, blood pressure, albuminuria, smoking, and LDL cholesterol. Nonetheless, despite having all risk factors at target, persons with type 1 diabetes still had 82% to 97% elevated risk of myocardial infarction and heart failure respectively. For every incremental risk factor not at target, the excess risk of death in cardiovascular outcomes increased in a graded fashion.

In conclusion, there was a steep graded association between decreasing number of cardiovascular risk factors at target and major adverse cardiovascular outcomes with patients with type 1 diabetes. While achievement of current evidence based target levels of five cardiovascular risk factors markedly reduced or even potentially eliminated the excess mortality risk, these patients remained at higher risk of myocardial infarction and heart failure compared with controls.

The final paper suggests that hemodynamic guided heart failure management may be beneficial in general clinical practice and not just in the context of controlled trials. In this study by Dr. Heywood and colleagues from Scripps Clinic Torrey Pines in La Jolla, California, the authors examined the first 2,000 patients implanted with the novel Pulmonary Artery Pressure Sensor, CardioMEMS, in the general cardiology practice setting.

They found that patients uploaded information an average of every 1.2 days, and that pressures were significantly reduced by remote monitoring using the Pulmonary Artery Sensor where patients with the highest mean pulmonary artery pressures had the highest reduction in pressures. Furthermore, they found that these general use patients experienced a greater reduction in

pulmonary artery pressure over time compared to those in the pivotal CHAMPION clinical trial.

The results from this large observational study, therefore, demonstrates hemodynamic heart failure management may be effective in U.S. clinical practice with high rates of patient adherence and effective pressure management.

This paper is accompanied by an excellent editorial by Drs. Gorter, Rienstra, and van Veldhuisen from University Medical Center, Groningen, Netherlands, which really places this paper in the clinical context of heart failure and particularly patients with heart failure and preserved ejection fraction

Well that wraps it up for your summaries. Now for our feature discussion.

We're discussing a hugely important emerging issue today. And it's MINOCA, a myocardial infarction with non-obstructive coronary arteries, and a very important paper in today's issue, which really provides the first insight into potential long-term medical therapy in the management of MINOCA.

However, now this issue of MINOCA is quite new and I'm sure new to many of those listening on the line. So, I am with the first and corresponding author of the paper, Dr. Bertil Lindahl from Uppsala Clinical Research Center in Sweden. Welcome.

Dr Bertil Lindahl: Thank You.

Dr Carolyn Lam: And also the associate editor who managed this paper, Dr. Gabriel Steg from Hospital Bichat in Paris, France. Welcome back.

Dr Gabriel Steg: Hello.

Dr Carolyn Lam: Now, we need to start by first understanding what we're talking about. MINOCA ... give us a good definition of what you mean by MINOCA. And does it include the non-coronary causes of AMI, or non-obstructive disease? Does it include myocarditis? Does it include the non-cardiac causes, like pulmonary embolism?

Dr Bertil Lindahl: Our definition of MINOCA used in this paper is that you received the ICD code for acute myocardial infarction. If you have a clinically clear case of myocarditis or Takotsubo and were not included in this analysis. But we know if we look into patients that have got the diagnosis of myocardial infarction ... if you performed, for instance, MRI afterward, you can see that a portion of the patients experience ... between 10 and 30 percent of the MINOCA patients, have evidence of myocarditis, although it was not clinically expected.

So this is a heterogeneous population ... initial diagnosis was myocardial infarction.

Dr Carolyn Lam: Thank you for clarifying what you used in your study. Gabriel, could I just, you know, bring you in on this because you invited an excellent editorial that accompanies this paper. And, basically, it helps to get us past all this terminology you know, MINOCA now. Could you maybe just clarify the overall perspective of what it means?

Dr Gabriel Steg: Yeah. This area is fairly new and we still have a major nomenclature problem. Clearly it's been recognized for many years that patients who have a clinical syndrome of myocardial infarction do not necessarily have obstructive coronary artery disease. At least severe obstructive coronary artery disease. Many patients have mild lesions and some patients apparently have no lesion at all.

Now, over the last few years we've understood that this is really a syndrome. And that under that big umbrella, there are patients who have non-cardiac causes of troponin elevation and chest pain. These should be excluded from MINOCA. If you have pulmonary embolism, this is not MINOCA. This is pulmonary embolism.

The second aspect is there are more subtle distinctions to be made with fairly new entities such as Takotsubo. When this study was started, Takotsubo was an emerging disease concept. And so the authors were not able to properly rule out the Takotsubos and probably a few myocarditis from their data set. We now have learned over the past few years that MRI is an excellent tool to screen MINOCA patients and flush out patients who have myocarditis or Takotsubo, which are not rare. Actually it's a substantial portion of that entity.

And then we're left with what I call the true MINOCA. Now what's fascinating in the study here is really that ... first of all I want to say this is another great study from our Swedish colleagues leveraging their data collection tools, which are remarkable. Really an example to the world.

The second thing is they have collected ten years of data on MINOCA. And they're able to tease out which are the agents that should be using secondary prevention in that population. Elegantly demonstrating with sensitivity analysis and positive and negative controls what are the agents associated with improved outcomes and what are the agents that apparently do not impact outcomes.

So even though at the time they were not able to rule out myocarditis and Takotsubo properly, still the sheer size of their study, long term follow up, and the careful statistical analysis that they've done are remarkable.

Dr Carolyn Lam: I couldn't agree more. And more so in an area that is really emerging in importance. And for which we don't have any prospective clinical trials. I'm correct in saying that, right? So Bertil, this would be a great point for you to let us know what are the main findings from your study please.

Dr Bertil Lindahl: The main findings are that statins are associated with a beneficial effect on the cardiac event. And also, ACE inhibitors or ARBs, while we were not able to show statistically things you can affect with beta blockers and similarly not with dual anti-platelet treatment. So that's basically the main findings of the study.

Dr Carolyn Lam: May I ask how have these findings personally impacted your clinical practice or do you think the next steps are gaps that need to be addressed first?

Dr Bertil Lindahl: I think that's an ongoing discussion in Sweden now and in our hospital on how this should be applied to clinical practice. Nothing. It will have an effect that statins and ACE Inhibitors or ARBs will be used. I'm not sure whether we still can say that we should not use beta blockers or dual antiplatelet treatment. But I think also that we are now discussing we should do a randomized clinical trial to really tease out whether we should use beta blockers or not or also verifying the findings regarding ACE Inhibitors and ARBs.

So, I think there's always a discussion whether we can really use observation studies for treatment decision. But I think since we don't have any better trials so far I think that this is the best that we can get. So I think it will be used and applied in clinical practice.

Dr Carolyn Lam: Indeed. I really agree with what Gabriel said this is the best available evidence we have now. And my personal take home message was to pay more attention to the statins and the ACE Inhibitors. So congratulations on this great study.

Gabriel, what do you think? What are next steps? I mean, MINOCA's not even in the guidelines now. Our guidelines talk about type 1, type 2, AMI ...how does it all fit in?

Dr Gabriel Steg: Well, we've seen a sea change in the concepts regarding myocardial infarction over the last fifteen years with the advent of troponin and the ability to diagnose new patients that previously we wouldn't even label as an MI.

The second aspect is we've recognized over the years that there are some genuine MI's that don't have severe obstructive coronary artery disease. Now what's interesting is that some of them may have apparently mild obstructive disease. Which presumably is related to coronary dissections, embolism, plaque rupture with thrombosis that disappeared in the interim. And some of them may have actually "clean" coronary arteries and have myocardial infarction related to other mechanisms such as micro vascular mechanisms. What's interesting, and I'd like to ask the opinion of Dr. Lindahl is, these three types of diseases; mildly obstructive disease, coronary dissection, and microvascular angina are all more frequent among women. And I wonder whether you have any insights regarding gender differences in your registry.

Dr Bertil Lindahl: In this study, in the sub-group analysis we saw no significant interaction between gender and the effects. But unfortunately we don't have the registry

information between , let's say completely "normal coronary arteries" versus "mildly obstructed coronary arteries". And that's a clear limitation of this study. It will be very interesting to see whether these effects are similar in these two sub-groups.

It seems from other studies that approximately fifty percent of the MINOCA patients that have normal coronary arteries and fifty percent that have mild aortic disease. So this is a limitation of this study and I think that's just something we have to look for in the future. And I hope that we will have in the registry onwards, data on whether this normal or mild coronary artery disease.

Dr Carolyn Lam: Really appreciate that and really appreciate the insights you gentlemen have shared. Any final words or concluding remarks, Gabriel?

Dr Gabriel Steg: Well, again congratulations on the great study. I would refer our readers to the excellent editorial of John Beltrame that accompanies this paper, which reviews the concepts of MINOCA, the nomenclature, and some of the remaining and lingering questions that plague the field. And delineates way forward for studies.

I think it's a fascinating area. I'm sure we're going to hear a lot more, both from the Swedish Heart Registry as well as other data sources. I think we all need to stay tuned to this important area. The prognosis of these patients is not so good, so we need to pay attention to that entity.

Dr Carolyn Lam: Wonderfully put. Well, thank you listeners for joining us this week. Please share this episode with all of your friends. So thank you and join us next week.