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A History of Systemic Hypertension and Incident Heart Failure Hospitalization in Patients with Acute Myocardial Infarction and Left Ventricular Systolic Dysfunction

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Abstract

The associations of a history of hypertension with subsequent outcomes after acute myocardial infarction (AMI) have not been examined in propensity-matched studies. Of the 6632 post-AMI patients with left ventricular systolic dysfunction in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 4407 had a history of hypertension. Propensity scores for a history of hypertension, estimated for each patient using 64 baseline characteristics, were used to match 1990 pairs of patients with and without a hypertension. Matched Cox regression models were used to estimate associations between hypertension and outcomes during 16 months of mean follow-up. HF hospitalization occurred in 11.9% and 8.8% patients respectively with and without hypertension (hazard ratio {HR} when hypertension was compared with no hypertension, 1.36; 95% confidence interval {CI}, 1.10–1.68; $P=0.004$). The association between a history of hypertension and HF hospitalization was only significant among patients without prior HF ($n=3495$; HR, 1.48; 95% CI, 1.18–1.84; $P=0.001$) but not in those with prior HF ($n=485$; HR, 1.09; 95% CI, 0.73–1.62; $P=0.688$; p for interaction=0.179). A history of hypertension was not associated with all-cause mortality (HR, 1.02; 95% CI, 0.86–1.22; $P=0.790$) or cardiovascular hospitalization (HR, 1.08; 95% CI, 0.92–1.27; $P=0.339$). In conclusion, a history of hypertension was associated with subsequent HF hospitalization post-AMI, especially among those without a prior history of HF, suggesting that hypertension increased the risk of hospitalization with incident HF but did not affect hospitalization due to worsening HF symptoms among those with prevalent HF.

Keywords

Hypertension; myocardial infarction; heart failure; morbidity; mortality

Acute myocardial infarction (AMI) and hypertension are associated with left ventricular remodeling and are risk factors for incident heart failure (HF).^{1–3} A history of hypertension

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may increase ventricular remodeling and the risk of HF after AMI.^{4,5} However, the association of a history of hypertension and incident HF has not been examined in a propensity-matched population of post-AMI patients with left ventricular systolic dysfunction (LVSD). We studied the effect of a history of hypertension on HF hospitalization in a propensity-matched cohort of post-AMI patients with LVSD, with and without prevalent HF, in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).

Methods

The design and results of EPHESUS, a multicenter, randomized, clinical trial of eplerenone have been previously reported.⁶ Briefly, 6632 post-AMI patients with LVSD (ejection fraction $\leq 40\%$) and HF symptoms were randomized to receive eplerenone or placebo, and were followed for up to 2.5 years. Patients with serum creatinine >2.5 mg/dL or potassium >5.0 mEq/L were excluded. Patients were receiving standard medical therapy including an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (87%) and beta blockers (75%).

Of the 6632 EPHESUS participants, 4007 (60%) patients had hypertension and 975 (15%) had HF at baseline. Data on baseline history of hypertension were collected by study investigators and were available for all patients. Hospitalization due to HF is the primary outcome of the current analysis and was a secondary outcome in EPHESUS. Because patients with HF are more likely to have HF hospitalization, data were separately analyzed for all patients and those without prevalent HF for incident HF hospitalization. We also examined the association of a history of hypertension with other EPHESUS outcomes. The cause of death and primary diagnosis leading to hospitalization were adjudicated by an EPHESUS critical-events committee, members of which were blinded to the patient's study drug assignment.

Because of the imbalances in baseline covariates between patients with and without a history of hypertension, we used propensity score matching to assemble cohorts of patients who would be well-balanced in all measured covariates.^{7,8} At first, we separately estimated propensity scores for a history of hypertension for all 6632 patients and 5657 patients without prevalent HF. We used the same non-parsimonious multivariable logistic regression model for both cohorts.^{9,10} For the all-patient model, we used the 64 baseline covariates displayed in Figure 1, and for the incident HF model, we excluded the baseline HF variable. Using a greedy matching protocol, we then matched 1990 pairs of patients (1721 pairs of those without baseline HF) with and without a history of hypertension who had similar propensity scores.^{10,11} We assessed the efficiency of matching by estimating between-group pre- and post-match absolute standardized differences for all measured baseline covariates, and presented them as Love plots.¹¹⁻¹³ An absolute standardized difference of 0% indicates no bias and $<10\%$ indicates inconsequential bias.

We used Kaplan-Meier plots and matched Cox regression analyses to estimate association between hypertension and HF hospitalization in all patients and in those without prevalent HF. To determine if the association between history of hypertension and new-onset HF hospitalization was homogeneous across various subgroups, we conducted subgroup analyses with formal testing for interactions. We confirmed the assumption of proportional hazards by a visual examination of the log (minus log) curves. All statistical tests were evaluated using two-tailed 95% confidence levels, and data analyses were performed using SPSS-15 for Windows.¹⁴

Results

Imbalances in baseline characteristics before matching and balances achieved after matching between patients with and without a history of hypertension are displayed in Tables 1 and Figure 1. After matching, all 64 measured baseline covariates were well-balanced between the groups. Post-match absolute standardized differences were <10% for all measured covariates and <5% for most covariates, suggesting substantial bias reduction (Figure 1).

Among the 3980 matched post-AMI patients, a total of 413 (10.4%) patients had a hospitalization due to HF during 16 months of mean follow-up. HF hospitalization occurred in 237 (11.9%; rate, 984/10000 person-years) and 176 (8.8%; rate, 717/10000 person-years) patients respectively with and without a history of hypertension (hazard ratio {HR} when a history of hypertension was compared no history of hypertension, 1.36; 95% confidence interval {CI}, 1.10–1.68; $P=0.004$; Figure 2a and Table 2). Among matched patients, the association between a history of hypertension and HF hospitalization was significant only in patients without previous HF ($n=3,495$, HR 1.48, 95% CI 1.18 to 1.84, $p=0.001$), but not in those with previous HF ($n=485$, HR 1.09, 95% CI 0.73 to 1.62, $p=0.688$, p for interaction =0.179). Among the 6632 patients before matching, hypertension-associated increase in HF hospitalization was only significant among those without previous HF ($n=5,657$, propensity-adjusted HR 1.49, 95% CI 1.22 to 1.82, $p<0.0001$) but not among those with previous HF ($n=975$, propensity-adjusted HR 1.07, 95% CI 0.76 to 1.51, $p=0.683$; p for interaction =0.004). The associations of a history of hypertension with other outcomes are displayed in Table 3.

Among the 3442 matched patients without prior HF, all 64 measured baseline covariates were well-balanced between those with and without a history of hypertension (data not shown). Overall, 316 (9.2%) patients had hospitalization due to new-onset HF during 16 months of mean follow-up. Hospitalization due to incident HF occurred in 190 (11.0%; rate, 880/10000 person-years) and 126 (7.3%; rate, 598/10000 person-years) patients with and without a history of hypertension (HR when a history of hypertension was compared with no history of hypertension, 1.47; 95% CI, 1.15–1.88; $P=0.002$; Figure 2b and Table 2). The association between a history of hypertension and hospitalization due to new-onset HF was homogenous across a wide range of subgroups (Figure 3).

Discussion

The findings from the current analysis demonstrate that in a propensity-matched cohort of post-AMI patients with LVSD and HF symptoms, who were well-balanced in 64 baseline characteristics, including blood pressure, a history of hypertension was associated with increased HF hospitalization. The association between hypertension and HF hospitalization was only significant in subgroups of patients without prior HF suggesting that an antecedent hypertension may have an intrinsic association with left ventricular remodeling and development of HF in post-AMI patients with LVSD. The lack of an association of hypertension with overall mortality or cardiovascular hospitalization suggests that ventricular remodeling and development of HF constitute the initial cardiovascular pathogenic pathway after AMI. These findings are important as despite receipt of contemporary standard therapy, and well-balanced, well-controlled blood pressure, a history of hypertension was associated with HF hospitalization, an event associated with increased subsequent mortality.^{15,16}

Data from animal and human studies suggest that myocardial remodeling and poor outcomes after AMI may be mediated via an increase in blood pressure and afterload.^{17,18} However, our matched cohort had well-controlled blood pressure, which was well-balanced between

the groups. Left ventricular hypertrophy (LVH) is a risk factor for HF and is more common in those with hypertension.² We had no data on baseline LVH but its prevalence was likely low in these patients.^{19–21} Ventricular remodeling often precedes LVH,²² and it is possible that subclinical hypertensive heart disease (Stage B or pre-clinical HF), independent of blood pressure, LVH, or LVSD, may have predisposed these patients to increased risk of clinical HF (Stage C).²³ The intrinsic risk associated with hypertension in post-AMI patients is also evident from their response to therapy, which is often more pronounced in those with advanced disease and higher comorbidity burden.²⁴ In the EPHESUS trial, eplerenone-associated reduction in all-cause mortality was greater in patients with hypertension than in those without (p for interaction=0.05).^{6,25}

Findings of our study are consistent with those from other published work.^{5,18,26} In the Valsartan in Myocardial Infarction Trial (VALIANT), a history of hypertension was associated with HF hospitalization and cardiovascular mortality, but had no association with all-cause death.¹⁸ Patients in that study were also post-AMI with LVSD and HF symptoms, and 58% had baseline hypertension. Despite these similarities, our study is distinguished by propensity score matching based on 64 baseline characteristics including blood pressure. The lack of an association between hypertension and cardiovascular mortality in our study is likely due to shorter mean follow-up (16 month versus 24 months in VALIANT). Studies that demonstrated an association with mortality either had longer follow-up or did not adjust for all key prognostically important covariates.²⁷

Some findings from our subgroup analyses based on patients without prior HF deserve further discussion. Despite smaller relative risk, patients ≥ 65 years and those with ejection fraction $< 35\%$ had higher absolute risk of incident HF. Interestingly, despite a lower non-significant relative risk, the absolute risk for hypertension-related incident HF was higher in women, regardless of a history of hypertension. Our subgroup analyses suggest that the profile of a patient most likely to experience hypertension-related incident HF is that of a younger male with higher Killip class symptoms. The significant interaction between hypertension and the use of ACE inhibitors or angiotensin receptor blocker is likely due to chance. However, taken together, the higher hypertension-associated HF hospitalization among patients not receiving inhibitors of renin-angiotensin system or beta-adrenergic system highlights the importance of these drugs in post-AMI patients with LVSD and a history of hypertension.^{28–31} Despite similar hypertension-associated HF hospitalization regardless of the receipt of eplerenone, the absolute rates of HF hospitalization were lower in patients receiving eplerenone.

Our study has several limitations. Although data on history of hypertension were collected at baseline, this was not validated and misclassification is possible. It is also possible that patients without hypertension at baseline may have developed hypertension during follow-up. However, both random misclassification and regression dilution are known to underestimate true associations.³² Also, even though our propensity score model was based on 64 baseline covariates, unmeasured covariates such as LVH may in part explain our findings. In conclusion, in patients with AMI and LVSD, a history of hypertension was associated with subsequent increase in HF hospitalization, especially among those without prior HF, suggesting that hypertension increased the risk of hospitalization due to incident HF but did not affect hospitalization due to worsening HF symptoms in those with existing HF. Further studies need to develop and test interventions that would prevent HF hospitalization in post-AMI patients with a history of hypertension with well-controlled blood pressure and receiving appropriate neurohormonal blockade.

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References

1. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation* 1990;81:1161–1172. [PubMed: 2138525]
2. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, Gardin JM, Rutledge JE, Boineau RC. Predictors of congestive heart failure in the elderly: the Cardiovascular Health Study. *J Am Coll Cardiol* 2000;35:1628–1637. [PubMed: 10807470]
3. Ganau A, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992;19:1550–1558. [PubMed: 1534335]
4. Kamimori K, Yoshiyama M, Shimada Y, Iida H, Nakamura Y, Uchida E, Yoshida K, Jissho S, Fukuda S, Takeuchi K, Yoshikawa J. Antecedent hypertension interacts with adverse ventricular remodeling after myocardial infarction. *Osaka City Med J* 2004;50:53–59. [PubMed: 15819299]
5. Parodi G, Carrabba N, Santoro GM, Memisha G, Valenti R, Buonamici P, Dovellini EV, Antoniucci D. Heart failure and left ventricular remodeling after reperfused acute myocardial infarction in patients with hypertension. *Hypertension* 2006;47:706–710. [PubMed: 16520403]
6. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–1321. [PubMed: 12668699]
7. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.
8. Rubin DB. Using propensity score to help design observational studies: Application to the tobacco litigation. *Health Services and Outcomes Research Methodology* 2001;2:169–188.
9. Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007;99:393–398. [PubMed: 17261405]
10. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. *Eur Heart J* 2007;28:1334–1343. [PubMed: 17537738]
11. Ahmed A, Husain A, Love TE, Gambassi G, Dell'Italia LJ, Francis GS, Gheorghiade M, Allman RM, Meleth S, Bourge RC. Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur Heart J* 2006;27:1431–1439. [PubMed: 16709595]
12. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265–2281. [PubMed: 9802183]
13. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. *J Clin Epidemiol* 2001;54:387–398. [PubMed: 11297888]
14. SPSS. SPSS for Windows, Rel. 15. Chicago, IL: SPSS Inc., Chicago, IL; 2007.
15. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: the Framingham study. *Am J Cardiol* 1979;44:53–59. [PubMed: 453046]
16. Herlitz J, Waagstein F, Lindqvist J, Swedberg K, Hjalmarson A. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol Trial). *Am J Cardiol* 1997;80:40J–44J.
17. Kannel WB, Sorlie P, Castelli WP, McGee D. Blood pressure and survival after myocardial infarction: the Framingham study. *Am J Cardiol* 1980;45:326–330. [PubMed: 7355742]

18. Thune JJ, Signorovitch J, Kober L, Velazquez EJ, McMurray JJ, Califf RM, Maggioni AP, Rouleau JL, Howlett J, Zelenkofske S, Pfeffer MA, Solomon SD. Effect of antecedent hypertension and follow-up blood pressure on outcomes after high-risk myocardial infarction. *Hypertension* 2008;51:48–54. [PubMed: 18025296]
19. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002;106:3068–3072. [PubMed: 12473553]
20. Solomon SD, Janardhanan R, Verma A, Bourgoun M, Daley WL, Purkayastha D, Lacourciere Y, Hippler SE, Fields H, Naqvi TZ, Mulvagh SL, Arnold JM, Thomas JD, Zile MR, Aurigemma GP. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;369:2079–2087. [PubMed: 17586303]
21. Ahmed A, Perry GJ, Husain A. VALIDD should not invalidate angiotensin-receptor blockers. *Lancet* 2007;369:2053–2054. [PubMed: 17586284]
22. Chen-Izu Y, Chen L, Banyasz T, McCulle SL, Norton B, Scharf SM, Agarwal A, Patwardhan A, Izu LT, Balke CW. Hypertension-induced remodeling of cardiac excitation-contraction coupling in ventricular myocytes occurs prior to hypertrophy development. *Am J Physiol Heart Circ Physiol* 2007;293:H3301–H3310. [PubMed: 17873027]
23. Hunt, SA.; Abraham, WT.; Chin, MH.; Feldman, AM.; Francis, GS.; Ganiats, TG.; Jessup, ML.; Konstam, MA.; Mancini, DM.; Michl, K.; Oates, JA.; Rahko, PS.; Silver, MA.; Stevenson, LW.; Yancy, CW. American College of Cardiology; 2005 [Accessed on August 17, 2005]. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Web Site Available at: <http://www.acc.org/clinical/guidelines/failure/index.pdf>.
24. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 2005;365:176–186. [PubMed: 15639301]
25. Pitt B, Ahmed A, Love TE, Krum H, Nicolau J, Cardoso JS, Parkhomenko A, Aschermann M, Corbalán R, Solomon H, Shi H, Zannad F. History of hypertension and the effects of eplerenone in patients with acute myocardial infarction complicated by systolic heart failure. *Hypertension* (In Press: To be published in the August issue of the journal) 2008;52:271–278.
26. Kenchaiah S, Pfeffer MA, St John Sutton M, Plappert T, Rouleau JL, Lamas GA, Sasson Z, Parker JO, Geltman EM, Solomon SD. Effect of antecedent systemic hypertension on subsequent left ventricular dilation after acute myocardial infarction (from the Survival and Ventricular Enlargement trial). *Am J Cardiol* 2004;94:1–8. [PubMed: 15219499]
27. Fresco C, Avanzini F, Bosi S, Franzosi MG, Maggioni AP, Santoro L, Bellanti G. Prognostic value of a history of hypertension in 11,483 patients with acute myocardial infarction treated with thrombolysis. GISSI-2 Investigators. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *J Hypertens* 1996;14:743–750. [PubMed: 8793697]
28. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. *Circulation* 2004;109:201–206. [PubMed: 14707020]
29. Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, Fujii M, Taniguchi A, Hamatani T, Nozato Y, Kataoka K, Morigami N, Ohnishi M, Kinoshita M, Horie M. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 2003;107:2559–2565. [PubMed: 12732605]
30. van Kats JP, Duncker DJ, Haitsma DB, Schuijt MP, Niebuur R, Stubenitsky R, Boomsma F, Schalekamp MA, Verdouw PD, Danser AH. Angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor blockade prevent cardiac remodeling in pigs after myocardial infarction: role of tissue angiotensin II. *Circulation* 2000;102:1556–1563. [PubMed: 11004147]

31. Yoshiyama M, Omura T, Yoshikawa J. Additive improvement of left ventricular remodeling by aldosterone receptor blockade with eplerenone and angiotensin II type 1 receptor antagonist in rats with myocardial infarction. *Nippon Yakurigaku Zasshi* 2004;124:83–89. [PubMed: 15277726]
32. Clarke R, Shipley M, Lewington S, Youngman L, Collins R, Marmot M, Peto R. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;150:341–353. [PubMed: 10453810]

Figure 1.

Love plot for absolute standardized differences before and after propensity score matching comparing covariate values for patients with and without history of hypertension (ACE=angiotensin-converting enzyme; AMI=acute myocardial infarction)

2 (a)

Number of patients at risk by history of hypertension

Yes	1990	1657	1352	702	182
No	1990	1705	1378	700	177

2 (b)

Number of patients at risk by history of hypertension

Yes	1721	1507	1229	614	151
No	1721	1453	1180	629	162

Figure 2.

Kaplan-Meier plots for hospitalization due to heart failure by history of hypertension (HTN), for (a) all patients and (b) those without baseline heart failure (CI= confidence interval; HR=hazard ratio)

Figure 3. Association of history of hypertension (HTN) with hospitalizations due to incident heart failure (HF) in subgroups of propensity score matched patients without baseline HF (ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; CI=confidence interval; HR=hazard ratio)

Table 1
Baseline patient characteristics by use of history of hypertension, before and after propensity matching

n (%) or mean (±SD)	Before propensity matching			After propensity matching		
	History of hypertension		P value	History of hypertension		P value
	No (n = 2625)	Yes (n = 4007)		No (n = 1990)	Yes (n = 1990)	
Age (years)	61.8 (±12.2)	65.4 (±10.8)	<0.001	63.4 (±12)	63.3 (±11)	0.853
Women	542 (21%)	1376 (34%)	<0.001	483 (24%)	465 (23%)	0.511
Nonwhite race	252 (10%)	396 (10%)	0.705	196 (10%)	213 (11%)	0.401
Smoking status						
Current	1038 (40%)	1005 (25%)		658 (33%)	676 (34%)	
Never	794 (30%)	1798 (45%)	<0.001	688 (35%)	673 (34%)	0.295
Former	793 (30%)	1204 (30%)		644 (32%)	641 (32%)	
Duration of index acute myocardial infarction hospitalization, days	14 (±11)	16 (±9)	<0.001	14 (±12)	15 (±8)	0.506
ST elevation index acute myocardial infarction	2007 (77)	2696 (67)	<0.001	1463 (74)	1456 (73)	0.735
Time to randomization (days)	7 (±3)	7 (±3)	0.013	7 (±3)	7 (±3)	0.889
Reperfusion or revascularization therapy within 14 days of index acute myocardial infarction						
Coronary artery bypass graft	26 (1%)	44 (1%)	0.675	21 (1%)	21 (1%)	1.000
Percutaneous coronary interventions	732 (28%)	848 (21%)	<0.001	521 (26%)	523 (26%)	0.971
Thrombolysis	798 (30%)	978 (24%)	<0.001	563 (28%)	562 (28%)	1.000
Past medical history						
Acute myocardial infarction	618 (24%)	1185 (30%)	<0.001	531 (27%)	551 (28%)	0.499
Angina pectoris	801 (31%)	1934 (48%)	<0.001	716 (36%)	733 (37%)	0.575
Heart failure	265 (10%)	710 (18%)	<0.001	244 (12%)	241 (12%)	0.922
Heart failure hospitalization	149 (6%)	363 (9%)	<0.001	139 (7%)	134 (7%)	0.800
Diabetes mellitus	645 (25%)	1497 (37%)	<0.001	576 (29%)	554 (28%)	0.454
Medications						
Eplerenone	1336 (51%)	1983 (50%)	0.262	1029 (52%)	999 (50%)	0.358
Angiotensin-converting enzyme inhibitors	2161 (82%)	3455 (86%)	<0.001	1685 (85%)	1672 (84%)	0.595

n (%) or mean ($\pm$ SD)	Before propensity matching			After propensity matching		
	History of hypertension		P value	History of hypertension		P value
	No (n = 2625)	Yes (n = 4007)		No (n = 1990)	Yes (n = 1990)	
Angiotensin-receptor blockers	73 (3%)	143 (4%)	0.077	67 (3%)	62 (3%)	0.721
Beta-adrenergic receptor blockers	1968 (75%)	2993 (75%)	0.799	1502 (76%)	1516 (76%)	0.636
Nitrates	1448 (55%)	2671 (67%)	<0.001	1177 (59%)	1166 (59%)	0.740
Aspirin	2311 (88%)	3559 (89%)	0.329	1754 (88%)	1759 (88%)	0.841
Anti-platelet drugs	885 (34%)	1025 (26%)	<0.001	616 (31%)	635 (32%)	0.534
Anticoagulants	374 (14%)	734 (18%)	<0.001	320 (16%)	322 (16%)	0.965
Statins	1324 (50%)	1771 (44%)	<0.001	966 (49%)	955 (48%)	0.751
Digoxin	360 (14%)	644 (16%)	0.009	296 (15%)	296 (15%)	1.000
Loop diuretics	1328 (51%)	2333 (58%)	<0.001	1082 (54%)	1091 (55%)	0.797
Other diuretics	144 (6%)	396 (10%)	<0.001	122 (6%)	140 (7%)	0.266
Potassium supplements	395 (15%)	690 (17%)	0.019	323 (16%)	334 (17%)	0.673
Magnesium supplements	86 (3%)	174 (4%)	0.029	72 (4%)	76 (4%)	0.799
Alpha-blockers	15 (1%)	109 (3%)	<0.001	14 (1%)	17 (1%)	0.711
Calcium channel blockers	287 (11%)	778 (19%)	<0.001	253 (13%)	251 (13%)	0.961
Anti-arrhythmics	292 (11%)	490 (12%)	0.172	240 (12%)	221 (11%)	0.366
Glycoprotein IIb/IIIa blockers	24 (1%)	39 (1%)	0.809	19 (1%)	24 (1%)	0.533
Killip status						
I	388 (15%)	665 (17%)		310 (16%)	296 (15%)	
II	1781 (68%)	2496 (62%)	<0.001	1319 (66%)	1339 (67%)	0.657
III	368 (14%)	727 (18%)		298 (15%)	284 (14%)	
IV	88 (3%)	119 (3%)		63 (3%)	71 (4%)	
Body mass index (kg/m ²)	26 ($\pm$ 4)	28 ($\pm$ 5)	<0.001	27 ($\pm$ 4)	27 ($\pm$ 4)	0.355
Systolic blood pressure (mm Hg)	114 ($\pm$ 14)	123 ($\pm$ 17)	<0.001	116 ($\pm$ 14)	117 ($\pm$ 14)	0.451
Diastolic blood pressure (mm Hg)	70 ($\pm$ 10)	74 ($\pm$ 11)	<0.001	71 ($\pm$ 10)	71 ($\pm$ 10)	0.877
Heart rate (beats per minute)	75 ($\pm$ 12)	75 ($\pm$ 12)	0.147	75 ($\pm$ 12)	75 ($\pm$ 12)	0.960
Laboratory values						
Potassium (mEq/L)	4.3 ($\pm$ 0.4)	4.3 ($\pm$ 0.5)	0.412	4.3 ($\pm$ 0.4)	4.3 ($\pm$ 0.5)	0.522
Creatinine (mg/dl)	1.09 ($\pm$ 0.3)	1.15 ($\pm$ 0.3)	<0.001	1.11 ($\pm$ 0.3)	1.11 ($\pm$ 0.3)	0.699

n (%) or mean ($\pm$ SD)	Before propensity matching			After propensity matching		
	History of hypertension		P value	History of hypertension		P value
	No (n = 2625)	Yes (n = 4007)		No (n = 1990)	Yes (n = 1990)	
Glucose (mg/dl)	130 ($\pm$ 70)	137 ($\pm$ 65)	<0.001	132 ($\pm$ 63)	132 ($\pm$ 61)	0.880
Creatinine phosphokinase (mg/dl)	287 ($\pm$ 361)	257 ($\pm$ 333)	<0.001	277 ($\pm$ 349)	269 ($\pm$ 338)	0.469
Uric acid (mg/dl)	6.1 ($\pm$ 4)	6.7 ($\pm$ 10)	0.005	6.3 ($\pm$ 4.4)	6.3 ($\pm$ 2)	0.774
Total cholesterol (mg/dl)	191 ($\pm$ 46)	195 ($\pm$ 50)	0.002	193 ($\pm$ 46)	191 ($\pm$ 49)	0.346
Triglyceride (mg/dl)	163 ($\pm$ 102)	174 ($\pm$ 110)	<0.001	168 ($\pm$ 109)	168 ($\pm$ 105)	0.993
Hemoglobin (g/dl)	13.4 ($\pm$ 1.7)	13.3 ($\pm$ 1.7)	<0.001	13 ($\pm$ 2)	13 ($\pm$ 2)	0.914
White blood cell ($10^3/\mu$ L)	8.9 ($\pm$ 3)	8.7 ($\pm$ 3)	0.002	8.9 ($\pm$ 3)	8.9 ($\pm$ 3)	0.983
Platelet ($10^3/\mu$ L)	261 ($\pm$ 93)	255 ($\pm$ 84)	0.009	258 ($\pm$ 93)	258 ($\pm$ 86)	0.880
Left ventricular ejection fraction, (%)	33 ($\pm$ 6)	33 ($\pm$ 6)	0.001	33 ($\pm$ 6)	33 ($\pm$ 6)	0.915

Table 2

Association between a history of hypertension and first heart failure hospitalization

	Rate, per 10,000 person-years follow-up (% events / follow-up in years)		Rate difference* (per 10,000 person-years)	Hazard ratio (95% confidence interval)	P value
	No history of hypertension	History of hypertension			
<i>All patients</i>					
Before matching (n=6632)	(n = 2625)	(n = 4007)			
	662 (8.2 / 3248)	1097 (13.0 / 4750)	+ 435	1.63 (1.39–1.91)	<0.001
After matching (n=3980)	(n = 1990)	(n = 1990)			
	717 (8.8 / 2455)	984 (11.9 / 2408)	+ 267	1.36 (1.10–1.68)	0.004
<i>Patients without prior heart failure</i>					
Before matching (n=5657)	(n = 2360)	(n = 3297)			
	545 (6.9 / 2989)	936 (11.4 / 4029)	+ 390	1.70 (1.42–2.05)	<0.0001
After matching (n=3442)	(n = 1721)	(n = 1721)			
	598 (7.3 / 2107)	880 (11.0 / 2158)	+ 282	1.47 (1.15–1.88)	0.002

* Absolute rate differences were calculated by subtracting the rates of events in the group without a history of hypertension from those in the group with a history of hypertension (before values were rounded)

Table 3

Association between a history of hypertension and other endpoints

	Rate, per 10,000 person-years follow-up (% events / follow-up in years)		Rate difference* (per 10,000 person-years)	Hazard ratio (95% confidence interval)	P value
	History of hypertension				
	No history of hypertension (n = 2625)	History of hypertension (n = 4007)			
<i>Before matching (n=6632)</i>					
All-cause mortality	1097 (14.4 / 3437)	1254 (16.3 / 5222)	+ 157	1.14 (1.01–1.30)	0.040
Cardiovascular hospitalization or cardiovascular mortality	2072 (24.2 / 3060)	2797 (31.0 / 4447)	+ 725	1.33 (1.21–1.46)	<0.001
CV mortality	931 (12.2 / 3437)	1092 (14.2 / 5222)	+ 160	1.17 (1.02–1.34)	0.024
AMI mortality	224 (2.9 / 3437)	182 (2.4 / 5222)	– 42	0.81 (0.60–1.10)	0.171
CV hospitalization	1340 (15.6 / 3060)	1900 (21.1 / 4447)	+ 560	1.39 (1.24–1.57)	<0.001
AMI hospitalization	473 (5.9 / 3295)	600 (7.4 / 4953)	+ 126	1.26 (1.04–1.53)	0.019
<i>After matching (n=3980)</i>					
All-cause mortality	1176 (15.4 / 2602)	1165 (15.4 / 2636)	– 11	1.02 (0.86–1.22)	0.790
Cardiovascular hospitalization or cardiovascular mortality	2251 (25.9 / 2288)	2512 (28.7 / 2277)	+ 261	1.11 (0.97–1.27)	0.122
CV mortality	984 (12.9 / 2602)	994 (13.2 / 2636)	+ 10	1.06 (0.88–1.28)	0.531
AMI mortality	238 (3.1 / 2602)	144 (1.9 / 2636)	– 94	0.71 (0.47–1.09)	0.114
CV hospitalization	1495 (17.2 / 2288)	1647 (18.8 / 2277)	+ 152	1.08 (0.92–1.27)	0.339
AMI hospitalization	549 (6.8 / 2476)	496 (6.3 / 2521)	– 53	0.87 (0.66–1.15)	0.330

* Absolute rate differences were calculated by subtracting the rates of events in the group without a history of hypertension from those in the group with a history of hypertension (before values were rounded)