

Impact of alpha-adrenergic receptor antagonists use on outcomes in patients with heart failure. A post-hoc analysis using Polish National Health Fund database

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Abstract

Background: The alpha-adrenolytics (AA) are not recommended in patients with ejection fraction (EF) reduced heart failure due to safety concerns. The aim of our study was to assess the safety of AA in patients hospitalized due to exacerbation of HF and the influence of these drugs on long-term endpoints.

Material and methods: Data collected by the National Health Fund tracking all patient admissions and taking of the drug prescriptions throughout the entire country was used. Patients hospitalized due to HF exacerbation were included. The primary outcome variable was all-cause mortality and the secondary was the first readmission due to HF or all-cause death occurring more than 30 days after discharge.

Results: Of 140 668 patients hospitalized in the year 2013, 53 317 were included and followed for a median of 56.3 months. AA patients had lower long-term all-cause mortality (52.8% vs. 54.9%, unadjusted $p = 0.038$). The treatment with AA positively and independently affected long-term survival [adjusted hazard ratio (adjHR): 0.82, 95% confidence interval (CI): 0.78–0.87, $p < 0.001$], as well as secondary endpoint (adjHR: 0.85, 95% CI: 0.81–0.90, $p < 0.001$). Cox analysis in the subgroup treated with beta-blockers revealed that treatment with AA was associated with lower mortality (adjHR: 0.82, 95% CI: 0.75–0.90, $p < 0.001$) and lower incidence of secondary endpoint (adjHR: 0.85, 95% CI: 0.78–0.92, $p < 0.001$).

Conclusion: In compliant patients hospitalized due to HF exacerbation post discharge treatment with AA was safe and beneficial.

Key words: heart failure treatment; alpha-blockers; mortality; readmissions

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Introduction

The alpha-adrenolytics (AA) are currently not recommended in patients with ejection fraction (EF)

reduced heart failure because of the safety concerns resulting from neurohormonal activation, fluid retention and exacerbating heart failure [1]. These drugs were also shifted to fourth line treatment of hyper-

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tension [2]. The above guidelines recommendations are primarily driven by the results of a well-known Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial that revealed the incidence of heart failure (HF) nearly doubled in doxazosin group compared with chlorthalidone group in patients treated for hypertension [3]. Some observational studies in elderly patients with hypertension also pointed to the at least double risk of development of HF related to the monotherapy with AA comparing thiazides [4, 5].

However, newer observations revealed no harm related to the AA treatment in HF [6], and recently propensity-score analysis of a large cohort of one institution disclosed the reduction of mortality in HF with the AA treatment [7].

AA are the drugs used most commonly for male lower urinary tract symptoms (LUTS) treatment, disregarding whether or not related to benign prostatic enlargement (BPE) and are considered the first-line drug treatment for men with moderate-to-severe LUTS according to the European Association of Urology (EAU) guidelines [8]. In the cross-sectional study of 122,630 elderly U.S. Medicare beneficiaries with HF, BPE occurred in 6% of men [9].

Therefore, the aim of our study was to assess the safety of AAs in patients hospitalized due to exacerbation of HF and the influence of these drugs on long-term all-cause mortality and combined endpoint consisting with mortality and readmissions due to exacerbations of HF in large database including the cases all-over the country.

Material and methods

We used data collected by the National Health Fund (NHF), the only public and obligatory health insurer in Poland. The NHF is practically the single payer that signs contracts with public and private healthcare providers.

The NHF database tracks all patient admissions, main diagnoses and taking of the drug prescriptions longitudinally throughout the entire country. The database also includes birth and death dates. The database search included the period from Jan 1st 2012 to December 31st 2018.

Inclusion criteria were patients who were hospitalized with International Classification of Diseases Tenth Revision (ICD-10) diagnosis code of I50 (congestive heart failure) due to HF exacerbation (specific NHF codes) in the 2013 year. We excluded patients who were hospitalized with the ICD-10 code I50 in the previous year disregarding the main

reason for the hospitalization as well as the patients who died during and within 30 days after the index hospitalization. We also excluded patients who had not bought any prescribed HF drugs including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), aldosterone receptor antagonists (MRA) or beta-blockers (BB) within period of 30 days after the index hospitalizations. The earliest procedure was considered the index one.

The primary outcome variable was all-cause mortality and the secondary was the first readmission due to HF or all-cause death occurring more than 30 days after discharge.

Survival analysis was performed for primary and secondary outcomes adjusting for age, sex, duration of the index hospitalizations, severe HF as reported to NFH (defined as need for vasopressors or dialysis), taking the prescription for the selected drugs during 30 day period following the discharge. The following medication was included into the analysis: AA, ACEi and/or ARB, MRA, BB, any diuretic, digoxin, dihydropyridine calcium channel blocker (CCB), nitrates, antiplatelets other than acetylsalicylic acid (ASA), anticoagulants [vitamin K (VKA) or non-vitamin K antagonist oral anticoagulant (NOAC)], statins, antidiabetics. All-cause mortality outcomes were censored at the end of the study on December 31st 2018. All data released from NHF were fully anonymized by applying encrypted personal identifiers before the authors had any access to them.

Statistics

Variables were compared using Fisher's exact test and Mann-Whitney U test. Estimates of cumulative event rates were calculated by means of the Kaplan-Meier method with the log-rank comparison of survival curves. Cox proportional-hazards analyses were performed for primary and secondary outcomes. The covariates for the models were selected using criteria of $p < 0.1$ in univariate analysis among above mentioned variables. Additional subanalysis was also performed by repeating the calculations in patients who received BB.

In BB subanalysis, treatment with carvedilol (or not) and treatment with HF approved BB (carvedilol, metoprolol, bisoprolol or nebivolol) were additionally analyzed.

P-values of less than 0.05 were considered significant. The statistical analysis of the data was performed using R (R version 3.6.1, R-core Team, R Foundation for Statistical Computing, Vienna, Austria, 2019, <https://www.r-project.org>), graphs with "survminer" and "forestmodel" R packages.

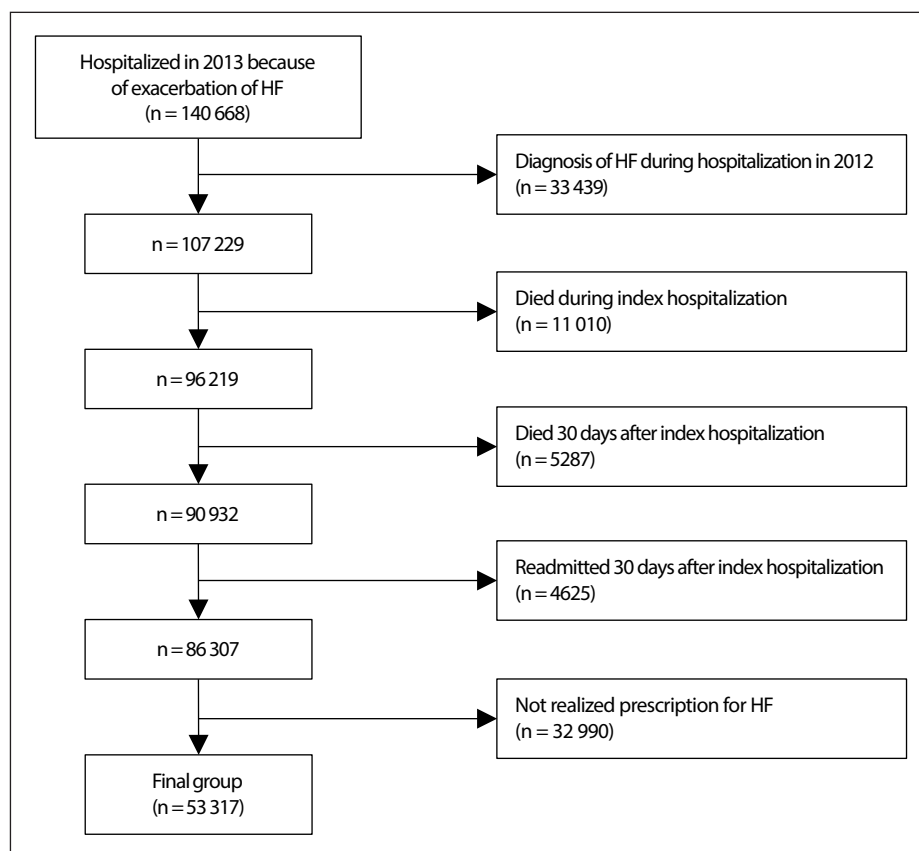


Figure 1. The flowchart of patient selection. HF — heart failure

The study was not considered for review by the local ethical committee since the database was previously collected by a government agency and all data were fully anonymized, and fully encrypted before the authors had any access to them. Moreover, there was no direct patient contact whatsoever.

Results

Of 140 668 patients who were hospitalized because of HF in the year 2013, 53 317 were included in the final analysis. Figure 1 presents the flowchart of patient selection, Table 1 characteristics of all patients included in the final analysis. Patients were followed for a median of 56.3 months [interquartile range (IQR): 43.2 months]. Primary outcome (long-term all-cause mortality) occurred in 29 226 (54.8%) and secondary outcome (combined long-term mortality with readmissions) in 34 319 (64.4%) overall. The group treated with non-selective alpha-adrenolytics (AA) consisted of 2436 of patients who were significantly older and more frequently men as compared with 50 881 patients not treated with AA (nonAA group) (Tab. 1). Most

of the patients ($n = 2409$; 98.9%) were treated with doxazosin, the remaining with terazosin. Selective alpha blockers were used in a small number of all patients — 1898 (3.6%) — with no significant difference between the compared groups.

The duration of hospital stay differed marginally, and the proportion of advanced HF was the same in both groups. The treatment assessed with filling the prescriptions differed between the groups, with significantly higher use of ACEi/ARB, CCB, nitrates, statin, antidiabetic drugs and lower usage of MRA, diuretics, digoxin, anticoagulants in AA group (Tab. 1). The proportion of patients treated with BB and antiplatelets (excluding ASA) was the same in both groups.

Primary end-point

AA patients had lower long-term all-cause mortality [$n = 1285$ (52.8%) *vs.* $n = 27941$ (54.9%), $p = 0.038$ for crude mortality]. One year all-cause mortality was already lower in AA group [$n = 8381$ (16.5%) *vs.* $n = 340$ (14.0%), $p < 0.001$ for crude mortality].

All-cause mortality trends over time are presented in Figure 2A with respective significant log-rank P

Table 1. Characteristics of the total group

	All patients	Without AA	AA	p
N	53 317	50 881	2436	
Age [yrs]	78.0 (13.0)	78.0 (13.0)	77.0 (712.0)	0.001
Females	29766 (55.8%)	29236 (57.5%)	530 (21.8%)	< 0.001
Hospital stay [days]	7.0 (4.0)	7.0 (5.0)	7.0 (4.0)	0.032
Advanced HF	2455 (4.60%)	2344 (4.61%)	111 (4.56%)	0.947
RASI	39507 (74.1%)	37619 (73.9%)	1888 (77.5%)	< 0.001
MRA	23356 (43.8%)	22416 (44.1%)	940 (38.6%)	< 0.001
BB	22023 (41.3%)	21024 (41.3%)	999 (41.0%)	0.777
Diuretics	29550 (55.4%)	28102 (55.2%)	1448 (59.4%)	< 0.001
Digoxin	7397 (13.9%)	7183 (14.1%)	214 (8.78%)	< 0.001
CCB	9680 (18.2%)	8864 (17.4%)	816 (33.5%)	< 0.001
Nitrates	5614 (10.5%)	5312 (10.4%)	302 (12.4%)	0.002
Antiplatelets	1672 (3.14%)	1592 (3.13%)	80 (3.28%)	0.711
Anticoagulant	9944 (18.7%)	9533 (18.7%)	411 (16.9%)	0.023
Statins	20706 (38.8%)	19564 (38.5%)	1142 (46.9%)	< 0.001
Antidiabetics	13857 (26.0%)	12988 (25.5%)	869 (35.7%)	< 0.001

BB — beta-blockers; AA — alpha-adrenolytics; RASI — renin–angiotensin system inhibitors (converting enzyme inhibitor and/or angiotensin receptor blocker); MRA — aldosterone receptor antagonists; CCB — dihydropyridine calcium channel blockers. Data presented as numbers (percentages) or medians (IQRs)

values for the comparison of Kaplan-Meier curves. Cox analysis revealed that the treatment with AA positively and independently affected long-term survival (adjHR: 0.82, 95% CI: 0.78–0.87, $p < 0.001$). The analysis also disclosed age, gender, duration of hospitalization, and most of concomitant medications as independent covariates of long-term mortality (Fig. 3A).

Secondary-end point

Readmissions combined with mortality occurred less frequently in AA than in nonAA group [$n = 1527$ (62.7%) *vs.* $n = 32\,792$ (64.4%), $p = 0.079$ for crude data].

The incidence of one year secondary-endpoint was lower in AA group [$n = 11\,475$ (22.6%) *vs.* 487 (20.0%), $p = 0.0039$ for crude data].

Secondary-endpoint trends over time are presented in Figure 2B with respective significant log-rank P values for comparison of Kaplan-Meier curves. Cox analysis revealed that the treatment with AA positively and independently influenced secondary endpoint (adjHR: 0.85, 95% CI: 0.81–0.90, $p < 0.001$) with age, gender, duration of hospitalization, and most concomitant medications (Fig. 3B).

Sub-analysis in BB treated patients

Characteristics of a subgroup of patients who fulfilled prescription for BB was similar to that of

the total group with lower ACEi/ARB use (Tab. 2). In contrast to the total group, in the subgroup treated with BB no difference between AA and nonAA groups were observed regarding ACEi/ARB, diuretic or anticoagulant treatment.

The most frequently used BB was carvedilol ($n = 13\,022$; 59.1%), followed by metoprolol ($n = 3093$; 14.0%), nebivolol ($n = 2976$; 13.5%), bisoprolol ($n = 1153$; 5.24%) and other, non-HF-approved BB ($n = 1779$; 8.08%).

Carvedilol was more frequently used in AA group compared with nonAA group ($n = 12\,494$ (59.4%) *vs.* $n = 528$ (52.9%); $p < 0.001$) while non-significant difference in non HF approved BB was seen between the groups.

Primary endpoint occurred less frequently in AA group compared with nonAA group ($n = 553$ (55.4%) *vs.* $n = 12119$ (57.6%), $p = 0.162$ for crude data) (Fig. 2C). Cox analysis revealed that difference as significant (adjHR: 0.82, 95% CI: 0.75–0.90, $p < 0.001$), with age, gender, and most concomitant medications as independent covariates (Fig. 4A). Secondary endpoint occurred less frequently in AA group compared with nonAA group [$n = 648$ (64.9%) *vs.* $n = 14\,057$ (66.9%), $p = 0.202$ for crude data] (Fig. 2D). Cox analysis revealed that difference as significant (adjHR: 0.85, 95% CI: 0.78–0.92, $p < 0.001$), with age, gender, and most concomitant medications as independent covariates (Fig. 4B).

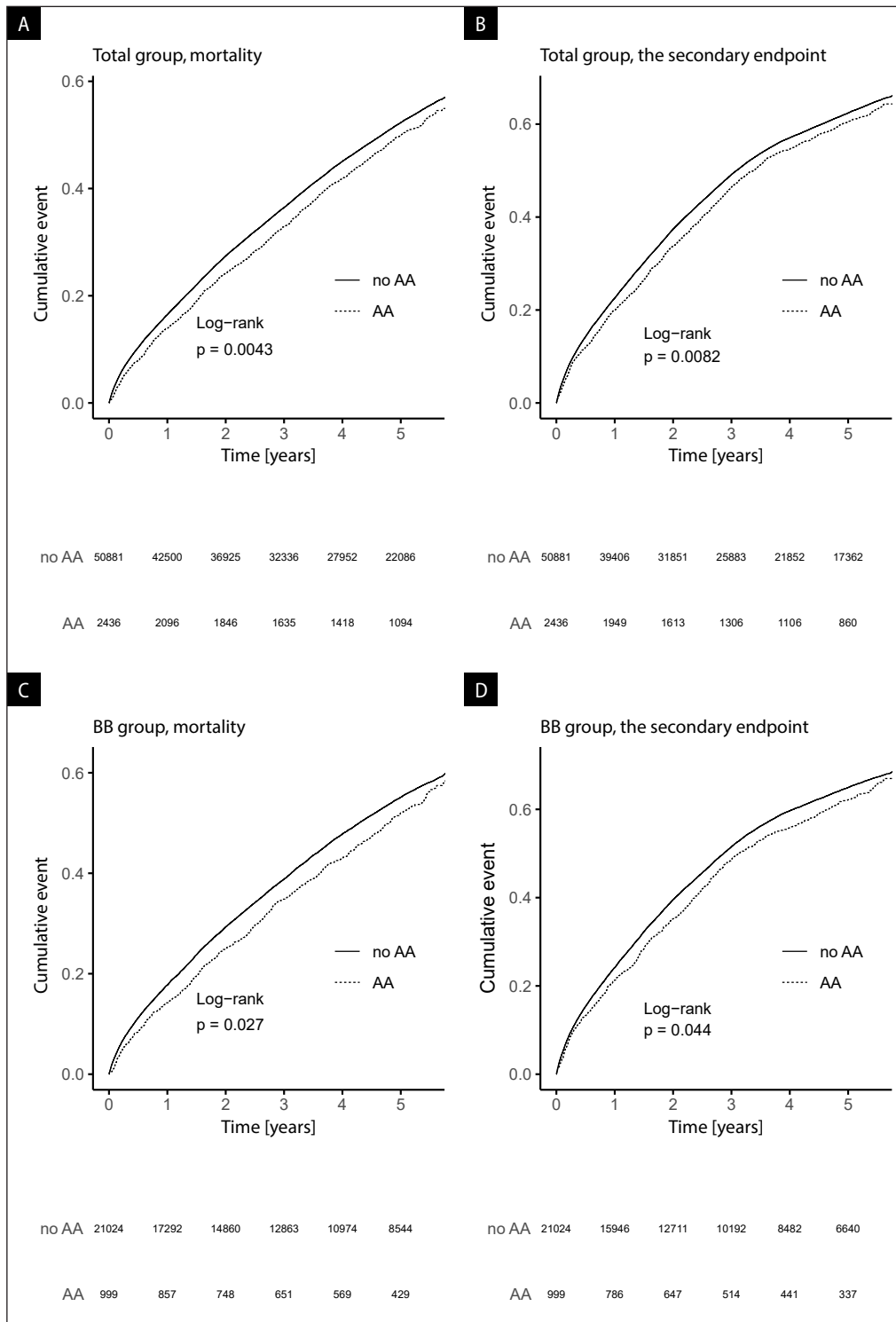


Figure 2. Primary (A) and secondary (B) endpoint in all patients, and beta-blocker (BB) treated patients respectively (C) and (D). AA — alpha-adrenolytics

Discussion

The results of our study revealed that in patients hospitalized all over the country in the year 2013 due to exacerbation of HF those additionally

treated with AA had 18% lower risk of all-cause death mortality and 15% lower risk of secondary endpoint (mortality or readmission) compared to the patients not treated with AA.

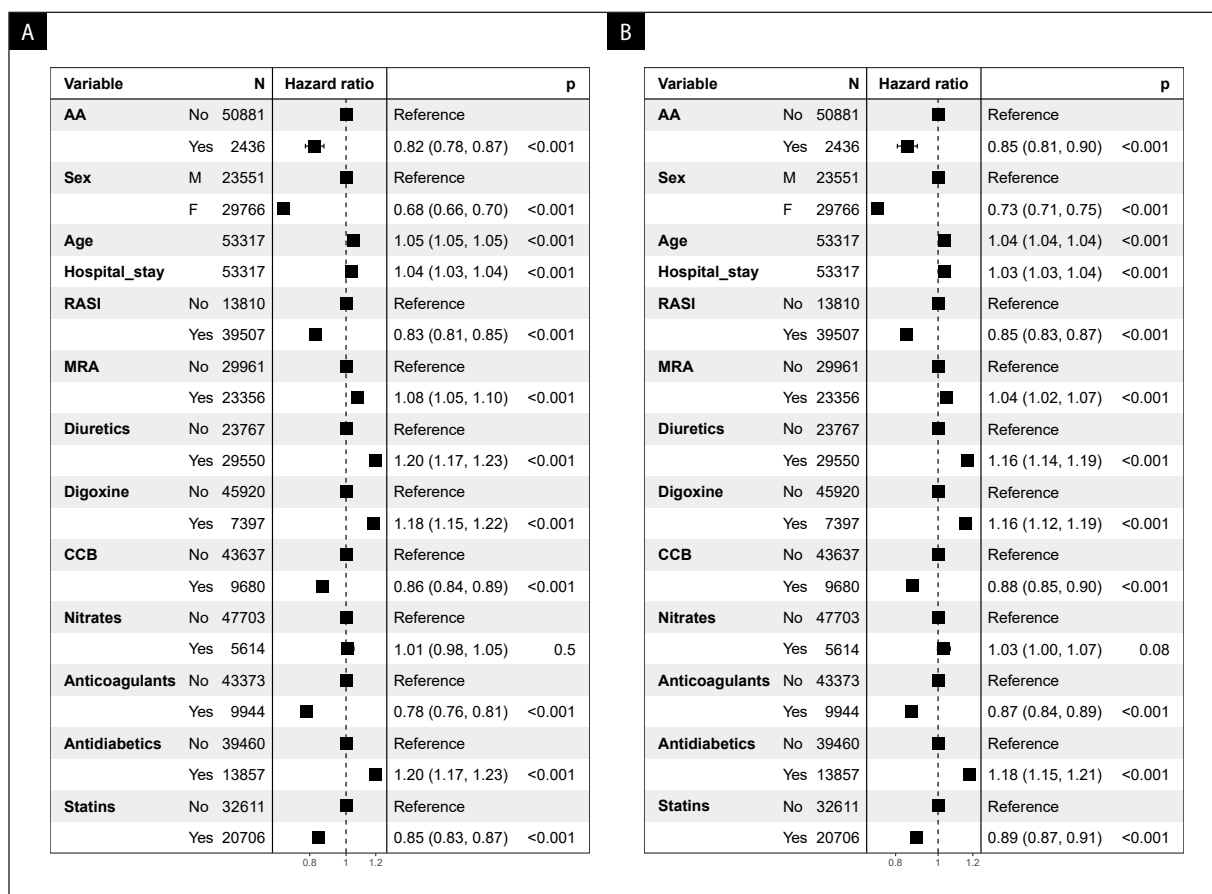


Figure 3. Cox analysis for primary (A) and secondary (B) endpoints in all patients. AA — alpha-adrenolytics; RASi — renin-angiotensin system inhibitors (converting enzyme inhibitor and/or angiotensin receptor blocker); MRA — aldosterone receptor antagonists; CCB — dihydropyridine calcium channel blockers

Table 2. Characteristics of subgroup treated with beta blockers

	All BB patients	BB without AA	BB with AA	p
N	22023	21024	999	
Age [yrs.]	78.0 (13.0)	78.0 (13.0)	77.0 (12.0)	0.012
Females	12031 (54.6%)	11834 (56.3%)	197 (19.7%)	< 0.001
Hospital stay [days]	7.0 (4.0)	7.0 (4.0)	7.0 (4.0)	0.164
Advanced HF	1083 (4.92%)	1029 (4.89%)	54 (5.41%)	0.513
RASi	13645 (62.0%)	12999 (61.8%)	646 (64.7%)	0.077
MRA	9203 (41.8%)	8835 (42.0%)	368 (36.8%)	0.001
Diuretics	12877 (58.5%)	12275 (58.4%)	602 (60.3%)	0.253
Digoxin	3442 (15.6%)	3342 (15.9%)	100 (10.0%)	< 0.001
CCB	3671 (16.7%)	3340 (15.9%)	331 (33.1%)	< 0.001
Nitrates	2587 (11.7%)	2442 (11.6%)	145 (14.5%)	0.006
Antiplatelets	749 (3.40%)	718 (3.42%)	31 (3.10%)	0.658
Anticoagulant	4355 (19.8%)	4169 (19.8%)	186 (18.6%)	0.369
Statins	8783 (39.9%)	8294 (39.5%)	489 (48.9%)	< 0.001
Antidiabetics	5903 (26.8%)	5534 (26.3%)	369 (36.9%)	< 0.001

BB — beta-blockers; AA — alpha-adrenolytics; RASi — renin-angiotensin system inhibitors (converting enzyme inhibitor and/or angiotensin receptor blocker); MRA — aldosterone receptor antagonists; CCB — dihydropyridine calcium channel blockers. Data presented as numbers (percentages) or medians (IQRs).

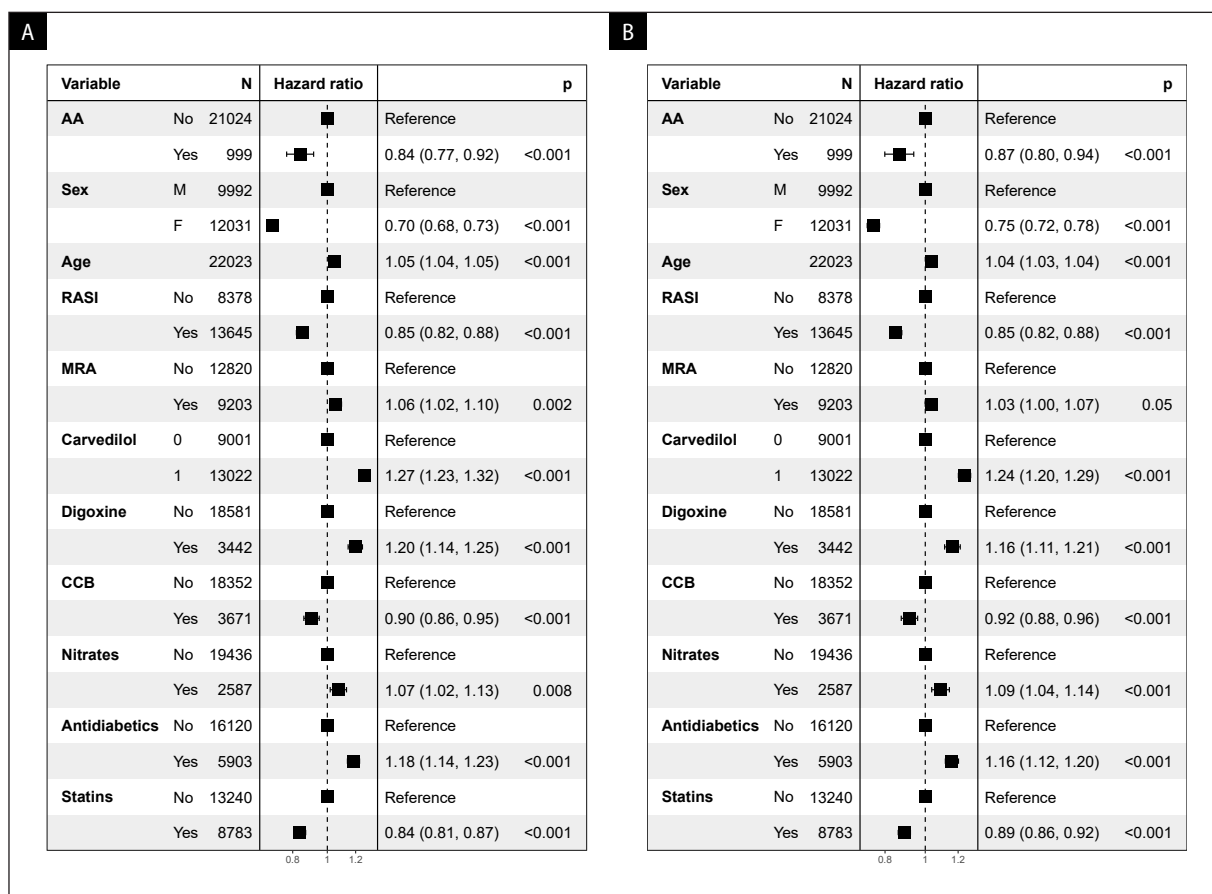


Figure 4. Cox analysis for primary (A) and secondary (B) endpoints in the subgroup treated with beta-blocker. AA — alpha-adrenolytics; RASI — renin angiotensin system inhibitors (converting enzyme inhibitor and/or angiotensin receptor blocker); MRA — aldosterone receptor antagonists; CCB — dihydropyridine calcium channel blockers

Compared to classic registry data, the patients in our study were 5 to 9 years older [10–17].

Balsam et al. analyzed 1415 hospitalized patients from Polish cohorts of both EURObservational Research Programme: The Heart Failure Pilot Survey (ESC-HF Pilot) and The European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) [17]. The mean age was lower (69 yrs) than in our cohort. Hypertension was diagnosed in 68.9%, coronary artery disease (CAD) in 43.6%, arterial fibrillation (AF) in 43.6% pts, diabetes in 35.1%, chronic kidney disease (CKD) 20.9%, chronic obstructive pulmonary disease (COPD) 18.8% of patients.

Despite the fact that only patients who purchased at least one of the classic drugs increasing survival were eligible for the study, in our cohort a lesser percentage of patients filled prescriptions for CV drugs when comparing treatment at discharge in mentioned above Polish cohorts of European registries. While the difference regarding ACEi and ARB was approximately 10%, and for MRA approx. 20%, in

case of BB, diuretics, digoxin, statins the percentage was two times smaller [17].

These differences may reflect the poor compliance and filling prescriptions among real-life HF patients.

Probably, some drugs were not prescribed at the time of discharge from hospital, possibly due to contraindications (hypotension, bradycardia, renal failure). Our cohort represents real life data and included exclusively patients with exacerbation of HF in contrast to registry studies that also included stable and outpatient HF patients and were conducted most often by selected centers of the tertiary level, often academic, so probably selecting patients with lower age, smaller number of concomitant diseases and with better compliance.

The in-hospital mortality was 2–3 times higher than in registry studies [11, 13, 17].

Similarly to other registers that included acute-HF patients, there was a high long-term mortality despite the fact that we excluded patients who died or were readmitted early [18, 19]. Also, one-year mor-

tality was 50% higher than reported in Polish cohorts of European registries [17].

On the other hand, patients who were not hospitalized with the diagnosis of heart failure during the previous year and who purchased at least one drug reducing the risk of death in HF within 30 days were enrolled, so the study group probably included more patients with *de novo* heart failure and cooperating well.

We decided to combine readmissions with total mortality as a secondary endpoint, since we have data on readmissions due to exacerbation of HF only but not total cardiovascular hospitalizations. Moreover, high mortality in our cohort interferes with assessment of other endpoints.

Unlike randomized drug trials conducted in HF, our group was not selected in terms of HF severity, New York Heart Association (NYHA) class, EF, etiology, renal function and other clinical parameters. Most of the randomized trials in HF have ruled out multiple coexisting chronic diseases, so the populations studied do not reflect well the patients treated in the hospital for worsening heart failure. The real-world data differs from randomized controlled trials (RCT) because of frequent exclusion of concomitant chronic conditions. In one analysis, 83% of RCT for heart failure excluded at least one chronic condition, including CAD, hypertension, stroke, AF, COPD, depression or dementia [20].

Results

The results of our study stays in contrast to the results of the ALLHAT study that disclosed nearly double the incidence of heart failure compared with chlorthalidone group in high risk hypertensive patients [3]. Although many authors explained the results of ALLHAT in doxazosin arm by the effect of neurohormonal activation from unopposed alpha receptor antagonism [21], others pointed to numerous limitations of the trial and issues needed to be addressed [22]. Systolic blood pressure was about 3 mm Hg higher in the doxazosin arm and increased incidence of heart failure in the doxazosin group was not accompanied by parallel increase in mortality. Moreover, the heart failure end-point in ALLHAT was much higher than that observed in other trials of similarly high-risk patients and the curves for heart failure incidence in the doxazosin and chlorthalidone groups separated within weeks after randomization with little further separation thereafter. Therefore, the treatment with doxaz-

osin may rather have unmasked occult heart failure while diuretic treatment would have been more likely to maintain control of signs and symptoms of preexisting heart failure [22].

The results of the Matsui et al.'s study assessing the benefits of adding bed-time dose of doxazosin for controlling morning blood pressure and the left ventricular structure and function in hypertensive patients were unequivocal [23].

In the doxazosin group, an increase in the left ventricular diameter was only seen in patients who did not take diuretics throughout the study. Authors conclude that the prior use of diuretics can prevent the unfavorable effects of doxazosin on the left ventricular structure. These observations can explain the results of early studies with AA in HF.

On the other hand, in a classical study comparing monotherapy with various 5 drugs in hypertensive men in the prazosin group there was no excess of oedema during more than one year follow-up, although the drug had also the highest rate of adverse effects leading to the termination of treatment [24].

In non-randomized analysis in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) that included almost 40 000 patient-years the addition of doxazosin to the hypertensive treatment resulted in BP lowering by approximately 12/7 mm Hg with achieving target BP in one third of participants with no apparent excess of heart failure [25].

The observations regarding the use of AA in hypertensive patients may not necessarily reflect well the use of these drugs in already treated HF.

In historical double-blind comparison of captopril and prazosin in HF, despite the maintained vasodilatation half of the 16 patients deteriorated after one month [26]. In our study, patients took (bought) at least one drug reducing mortality in heart failure. The study therefore tested the differences between adding AA as an additional drug to current therapy for heart failure, and did not compare AA with other classic drugs used in the treatment of HF.

The use of AA in a patient with HF in a situation where the drug is used to inhibit sympathetic activity and/or the RA system may not lead to excessive neurohormonal activation. The V-HeFT I trial revealed no differences in all-cause hospitalization between patients randomized to prazosin or hydralazine with isosorbide dinitrate or placebo in HF patients on background therapy of digitalis and diuretics [27].

The results of our study appear similar to the Jackevicius et al.'s study [7]. The authors performed the propensity score analysis of HF hospitalized in one institution from 2002 to 2015.

Of 169 911 patients who were hospitalized in the period of interest. 28% were on AA. The authors matched 35 715 pairs according to the AA treatment status using numerous covariates, unfortunately with the exception of the most important such as SBP and EF. The mean age of the matched group was lower (75 yrs) than in our study, and the usage of analyzed drugs was higher than in our group with the exception of ACEi or ARB which was similar and MRA which was higher in our group. The treatment with AA was associated with lower 2-year all-cause mortality in the whole group (42.8% versus 46.5% (HR: 0.93; 95% CI: 0.91 to 0.94; $p < 0.0001$)) and also in BB treated group (HR: 0.91; 95% CI: 0.89 to 0.92; $p < 0.0001$). Higher doses and nonselective AAs were also associated with lower mortality, regardless of BB treatment. These secondary analyses were performed in a very similar way as ours. Authors conclude that AAs may be used safely in HF patients where clinically indicated.

Another example suggesting the benefits of adding AA to the treatment of HF is the Carvedilol Or Metoprolol European Trial (COMET) that revealed a significant reduction in total and cardiovascular mortality with carvedilol compared with metoprolol [28].

Limitations of the study

Our study presents the typical limitations of a retrospective analysis of reimbursement data. Due to the limitations of the NHF database we were unable to assess many other important clinical parameters. In particular, evaluating patients in groups with preserved and reduced ejection fraction would be important. However, we had data on duration of hospitalization, advanced HF (requiring treatment with positive inotropes or renal replacement therapy) and post discharge treatment. We assume that including these covariates into analysis partially substitutes controlling on important clinical parameters or concomitant diseases. Some of the studies mentioned in the above discussion also did not control results on crucial data such as SBP or EF due to incompleteness [7].

Autopsies are rarely performed in Poland and a majority of deaths took place outside hospitals therefore we were unable to establish the cause of death.

A risk of potential errors or underreporting of diagnoses or procedures should also be taken into consideration.

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None.

Conflict of interest

None declared.

References

1. Ponikowski P, Voors AA, Anker SD, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016; 37(27): 2129–2200, doi: [10.1093/eurheartj/ehw128](https://doi.org/10.1093/eurheartj/ehw128), indexed in Pubmed: [27206819](https://pubmed.ncbi.nlm.nih.gov/27206819/).
2. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018; 39(33): 3021–3104, doi: [10.1093/eurheartj/ehy339](https://doi.org/10.1093/eurheartj/ehy339), indexed in Pubmed: [30165516](https://pubmed.ncbi.nlm.nih.gov/30165516/).
3. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2003; 42(3): 239–246, doi: [10.1161/01.HYP.0000086521.95630.5A](https://doi.org/10.1161/01.HYP.0000086521.95630.5A), indexed in Pubmed: [12925554](https://pubmed.ncbi.nlm.nih.gov/12925554/).
4. Bryson CL, Smith NL, Kuller LH, et al. Risk of congestive heart failure in an elderly population treated with peripheral alpha-1 antagonists. *J Am Geriatr Soc*. 2004; 52(10): 1648–1654, doi: [10.1111/j.1532-5415.2004.52456.x](https://doi.org/10.1111/j.1532-5415.2004.52456.x), indexed in Pubmed: [15450040](https://pubmed.ncbi.nlm.nih.gov/15450040/).
5. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and systemic hypertension treated with beta blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium antagonists, and alpha blockers. *Am J Cardiol*. 2002; 89(10): 1207–1209, doi: [10.1016/s0002-9149\(02\)02307-x](https://doi.org/10.1016/s0002-9149(02)02307-x), indexed in Pubmed: [12008178](https://pubmed.ncbi.nlm.nih.gov/12008178/).
6. Dhaliwal AS, Habib G, Deswal A, et al. Impact of alpha 1-adrenergic antagonist use for benign prostatic hypertrophy on outcomes in patients with heart failure. *Am J Cardiol*. 2009; 104(2): 270–275, doi: [10.1016/j.amjcard.2009.03.030](https://doi.org/10.1016/j.amjcard.2009.03.030), indexed in Pubmed: [19576359](https://pubmed.ncbi.nlm.nih.gov/19576359/).
7. Jackevicius CA, Ghaznavi Z, Lu L, et al. Safety of Alpha-Adrenergic Receptor Antagonists in Heart Failure. *JACC Heart Fail*. 2018; 6(11): 917–925, doi: [10.1016/j.jchf.2018.06.015](https://doi.org/10.1016/j.jchf.2018.06.015), indexed in Pubmed: [30316936](https://pubmed.ncbi.nlm.nih.gov/30316936/).
8. Abreu-Mendes P, Silva J, Cruz F. Pharmacology of the lower urinary tract: update on LUTS treatment. *Ther Adv Urol*. 2020; 12: 1756287220922425, doi: [10.1177/1756287220922425](https://doi.org/10.1177/1756287220922425), indexed in Pubmed: [32489425](https://pubmed.ncbi.nlm.nih.gov/32489425/).
9. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003; 42(7): 1226–1233, doi: [10.1016/s0735-1097\(03\)00947-1](https://doi.org/10.1016/s0735-1097(03)00947-1), indexed in Pubmed: [14522486](https://pubmed.ncbi.nlm.nih.gov/14522486/).
10. O'Connor CM, Stough WG, Gallup DS, et al. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail*. 2005; 11(3): 200–205, doi: [10.1016/j.cardfail.2004.08.160](https://doi.org/10.1016/j.cardfail.2004.08.160), indexed in Pubmed: [15812748](https://pubmed.ncbi.nlm.nih.gov/15812748/).

11. Yancy CW, Abraham WT, Albert NM, et al. OPTIMIZE-HF Investigators and Hospitals. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Arch Intern Med.* 2007; 167(14): 1493–1502, doi: [10.1001/archinte.167.14.1493](https://doi.org/10.1001/archinte.167.14.1493), indexed in Pubmed: [17646603](https://pubmed.ncbi.nlm.nih.gov/17646603/).
12. Sato N, Kajimoto K, Asai K, et al. ATTEND Investigators. Acute decompensated heart failure syndromes (ATTEND) registry. A prospective observational multicenter cohort study: rationale, design, and preliminary data. *Am Heart J.* 2010; 159(6): 949–955.e1, doi: [10.1016/j.ahj.2010.03.019](https://doi.org/10.1016/j.ahj.2010.03.019), indexed in Pubmed: [20569705](https://pubmed.ncbi.nlm.nih.gov/20569705/).
13. Adams KF, Fonarow GC, Emerman CL, et al. ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J.* 2005; 149(2): 209–216, doi: [10.1016/j.ahj.2004.08.005](https://doi.org/10.1016/j.ahj.2004.08.005), indexed in Pubmed: [15846257](https://pubmed.ncbi.nlm.nih.gov/15846257/).
14. Maggioni AP, Dahlström U, Filippatos G, et al. Heart Failure Association of the European Society of Cardiology (HFA), Heart Failure Association of ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2010; 12(10): 1076–1084, doi: [10.1093/eurjhf/hfq154](https://doi.org/10.1093/eurjhf/hfq154), indexed in Pubmed: [20805094](https://pubmed.ncbi.nlm.nih.gov/20805094/).
15. Maggioni AP, Dahlström U, Filippatos G, et al. Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail.* 2013; 15(7): 808–817, doi: [10.1093/eurjhf/hft050](https://doi.org/10.1093/eurjhf/hft050), indexed in Pubmed: [23537547](https://pubmed.ncbi.nlm.nih.gov/23537547/).
16. Chioncel O, Mebazaa A, Harjola VP, et al. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail.* 2017; 19(10): 1242–1254, doi: [10.1002/ejhf.890](https://doi.org/10.1002/ejhf.890), indexed in Pubmed: [28463462](https://pubmed.ncbi.nlm.nih.gov/28463462/).
17. Balsam P, Ozierański K, Kapłon-Cieślicka A, et al. Differences in clinical characteristics and 1-year outcomes of hospitalized patients with heart failure in ESC-HF Pilot and ESC-HF-LT registries. *Pol Arch Int Med.* 2019; 129: 106–116.
18. Lassus JPE, Siirilä-Waris K, Nieminen MS, et al. FINN-AKVA study group. Long-term survival after hospitalization for acute heart failure--differences in prognosis of acutely decompensated chronic and new-onset acute heart failure. *Int J Cardiol.* 2013; 168(1): 458–462, doi: [10.1016/j.ijcard.2012.09.128](https://doi.org/10.1016/j.ijcard.2012.09.128), indexed in Pubmed: [23073273](https://pubmed.ncbi.nlm.nih.gov/23073273/).
19. Younis A, Mulla W, Goldkorn R, et al. Differences in Mortality of New-Onset (De-Novo) Acute Heart Failure Versus Acute Decompensated Chronic Heart Failure. *Am J Cardiol.* 2019; 124(4): 554–559, doi: [10.1016/j.amjcard.2019.05.031](https://doi.org/10.1016/j.amjcard.2019.05.031), indexed in Pubmed: [31221464](https://pubmed.ncbi.nlm.nih.gov/31221464/).
20. Buffel du Vaure C, Dechartres A, Battin C, et al. Exclusion of patients with concomitant chronic conditions in ongoing randomised controlled trials targeting 10 common chronic conditions and registered at ClinicalTrials.gov: a systematic review of registration details. *BMJ Open.* 2016; 6(9): e012265, doi: [10.1136/bmjopen-2016-012265](https://doi.org/10.1136/bmjopen-2016-012265), indexed in Pubmed: [27678540](https://pubmed.ncbi.nlm.nih.gov/27678540/).
21. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Lancet.* 2000; 355(9207): 863–864, doi: [10.1016/s0140-6736\(00\)00092-1](https://doi.org/10.1016/s0140-6736(00)00092-1), indexed in Pubmed: [10752699](https://pubmed.ncbi.nlm.nih.gov/10752699/).
22. Poulter N, Williams B. Doxazosin for the management of hypertension: implications of the findings of the ALLHAT trial. *Am J Hypertens.* 2001; 14(11 Pt 1): 1170–1172, doi: [10.1016/s0895-7061\(01\)02212-9](https://doi.org/10.1016/s0895-7061(01)02212-9), indexed in Pubmed: [11724218](https://pubmed.ncbi.nlm.nih.gov/11724218/).
23. Matsui Y, Eguchi K, Shibasaki S, et al. Effect of doxazosin on the left ventricular structure and function in morning hypertensive patients: the Japan Morning Surge 1 study. *J Hypertens.* 2008; 26(7): 1463–1471, doi: [10.1097/HJH.0b013e3283013b44](https://doi.org/10.1097/HJH.0b013e3283013b44), indexed in Pubmed: [18551024](https://pubmed.ncbi.nlm.nih.gov/18551024/).
24. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med.* 1993; 328(13): 914–921, doi: [10.1056/NEJM199304013281303](https://doi.org/10.1056/NEJM199304013281303), indexed in Pubmed: [8446138](https://pubmed.ncbi.nlm.nih.gov/8446138/).
25. Chapman N, Chang CL, Dahlöf B, et al. ASCOT Investigators. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. *Circulation.* 2008; 118(1): 42–48, doi: [10.1161/CIRCULATIONAHA.107.737957](https://doi.org/10.1161/CIRCULATIONAHA.107.737957), indexed in Pubmed: [18559700](https://pubmed.ncbi.nlm.nih.gov/18559700/).
26. Bayliss J, Norell MS, Canepa-Anson R, et al. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. *Br Med J (Clin Res Ed).* 1985; 290(6485): 1861–1865, doi: [10.1136/bmj.290.6485.1861](https://doi.org/10.1136/bmj.290.6485.1861), indexed in Pubmed: [3924285](https://pubmed.ncbi.nlm.nih.gov/3924285/).
27. Loeb HS, Johnson G, Henrick A, et al. Effect of enalapril, hydralazine plus isosorbide dinitrate, and prazosin on hospitalization in patients with chronic congestive heart failure. The V-HeFT VA Cooperative Studies Group. *Circulation.* 1993; 87(6 Suppl): VI78–VI87, indexed in Pubmed: [8500244](https://pubmed.ncbi.nlm.nih.gov/8500244/).
28. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet.* 2003; 362(9377): 7–13, doi: [10.1016/S0140-6736\(03\)13800-7](https://doi.org/10.1016/S0140-6736(03)13800-7), indexed in Pubmed: [12853193](https://pubmed.ncbi.nlm.nih.gov/12853193/).