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Target Doses of Heart Failure Medical Therapy and Blood Pressure: Insights from the CHAMP-HF Registry

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Abstract

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Background: Patients with heart failure and reduced ejection fraction (HFrEF) are infrequently titrated to recommended doses of guideline-directed medical therapy (GDMT). The relationship between systolic blood pressure (SBP) and achieving GDMT target doses is not well studied.

Objective: To determine the rate of use of target doses of foundational GDMT in a contemporary cohort of patients with HFrEF across SBP categories.

Methods: Patients enrolled in the CHAMP-HF registry, without documented intolerance to ACE Inhibitors, (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor- neprilysin inhibitors (ARNI), and beta-blockers (BB) were assessed at enrollment. We estimated the proportion receiving target doses [% of target dose (95% confidence interval)] based on the most recent ACC/AHA/HFSA heart failure guidelines at baseline in all patients, and by SBP category (≥110 versus <110 mmHg).

Results: Of the 3095 patients eligible for analysis, 2421, (78.2%) had SBP ≥110 mmHg. The proportion of patients receiving target doses were 18.7% (17.3–20.0; BB), 10.8% (9.7–11.9; ACEI/ARB), and 2.0% (1.5–2.5; ARNI). Among those with SBP <110 mmHg (n= 674), 17.5% (14.6–20.4; BB), 6.2 % (4.4–8.1 ACEI/ARB), and 1.8% (0.8–2.8; ARNI) were receiving target doses. Among those with SBP ≥110 mmHg (n=2421), 19.0% (17.4–20.6; BB), 12.1% (10.8–13.4; ACEI/ARB), and 2.0% (1.5–2.6; ARNI) were receiving target doses.

Conclusions: In a large, contemporary registry of outpatients with chronic HFrEF eligible for treatment with BB and ACEI/ARB/ARNI, less than 20% of patients were receiving target doses, even among those with SBP ≥110 mmHg.

CONDENSED ABSTRACT

Beta blockers (BB), angiotensin receptor inhibitors/angiotensin receptor blockers (ACEI/ARB) and angiotensin-neprilysin inhibitor (ARNI) reduce mortality in patients with HFrEF, with the evidence suggesting a dose related benefit. Guidelines suggest titration to target doses among patients without intolerances. Systolic blood pressure (SBP) can be a limiting factor to intensifying HFrEF therapy, but the relationship between SBP and achieving target doses is unclear. The present study demonstrates that the prevalence those receiving target doses of ACEI/ARB/ARNI and BB was <20% across different SBP categories. This calls for increased efforts to optimize medication dosing in patients with HFrEF.

Keywords

heart failure; target dose; systolic blood pressure

Heart failure with reduced ejection fraction (HFrEF) is associated with significant morbidity and mortality (1). Over the past few decades, advances in medical therapy have resulted in a substantial reduction in poor cardiovascular outcomes (2-4). Although inhibition of the beta adrenergic system with beta-blockers (BB) and inhibition of the angiotensin pathway with ACE inhibitors (ACEI)/ angiotensin receptor blockers (ARBs) have been the cornerstone of HFrEF treatment(5), sacubitril/valsartan, which belongs to the class of angiotensin II receptor blocker-neprilysin inhibitors (ARNI), has recently been shown to provide additional morbidity and mortality reduction over enalapril alone among patients on background BB therapy (5,6).

In patients with HFrEF, target medication doses established in clinical trials are encouraged in national guidelines (5). This stems from evidence showing dose-related relationships between outcomes and ACEI (7) and BB doses (8,9). Despite this robust evidence, target doses of these important therapies are often underused in clinical practice (10,11). One potential barrier to intensifying guideline directed medical therapy (GDMT) may be concerns regarding low blood pressure, which can cause symptomatic hypotension and fatigue (12). Low blood pressure, as a barrier to achieving targeted dosing of GDMT in routine clinical care has not been described. Understanding whether blood pressure is a barrier to achieving targeted doses of HFrEF therapy can help guide how to achieve more aggressive dosing of evidence-based therapies. To address this gap, we used a large, multi-center, contemporary outpatient registry of patients with HFrEF to conduct an analysis to describe the intensity of HF medication dosing and to determine the proportion of patients in whom lower blood pressures might be a barrier to the intensification of ACEI/ARB/ARNIs or BBs.

Methods

Study Design

For this cross sectional analysis, we used data at enrolment from the CHAnge the Management of Patients with Heart Failure (CHAMP-HF) registry: a prospective, observational study of outpatients with HFrEF at 151 US practice sites (13). Patients eligible for enrollment met the following criteria: (1) age ≥ 18 years, (2) primary diagnosis of HFrEF (LVEF ≤ 40% within twelve months of enrollment), (3) prescribed ≥ 1 oral pharmacotherapy for HF at the time of enrollment, and (4) willingness to complete protocol requirements for study visits, procedures, and questionnaires. Patients were excluded if they were ineligible (actively participating in an interventional clinical research study, receiving comfort care measures only or enrolled in a hospice program, had a life expectancy of less than one year, and had a history of, or planned heart transplant, left ventricular assist device implantation, or dialysis). Additionally, we excluded those who reported HF medication-related side effects (new/worsening cough, worsening renal dysfunction, renal failure, angioedema, dizziness/lightheadedness/hypotension, clinically significant increase in serum potassium), had a known contraindication to ACEI/ARB, ARNI or BB, or were missing SBP and demographic information at enrollment.

Additional data collected at enrollment included patient-level demographics and clinical characteristics, medical history, laboratory results, use of HF medications and devices, and patient-reported health status. Eligible sites were identified based upon the completion of a feasibility survey, which provided investigators with the opportunity to ensure broad geographic and provider specialty representation. Study coordinators at each site were responsible for identification and enrollment of subjects during the course of a scheduled outpatient visit, with this analysis being limited to only those patients enrolled between December 2015 and August 2017. CHAMP-HF was sponsored by Novartis Pharmaceuticals Corporation, and all participating sites obtained local or central institutional review board approval prior to patient enrollment as well as informed consent from each participant.

Data Collection

Site coordinators interviewed patients to collect their sociodemographic characteristics and health status, and abstracted information from the medical record regarding medical history and medications at enrollment. The primary outcome for this analysis was the achievement of target dose beta blocker (≥100% target dose (yes/no)) and ACEI/ARB/ARNI (≥100% target dose (yes/no)), based on each patient's daily dose at enrollment compared with the guideline-recommended target daily doses (Supplemental Table 1)(5,14). We limited our analysis to these medication classes because, barring any intolerance, guidelines recommend all patients with HFrEF be placed on maximally tolerated (target) doses of these medications before considering additional therapy(14). Medication daily dose was calculated based on dose per administration and frequency. Systolic blood pressure readings were obtained from the patients' baseline clinic visit as was routine for each participating site.

Statistical Analysis

The enrollment characteristics of the CHAMP-HF cohort were stratified by SBP categories (<110 versus ≥ 110 mmHg). We used proportions for categorical variables and medians with quartiles for continuous variables. We calculated the proportion of patients receiving ACEI/ARB/ARNI and BBs in the overall cohort and by SBP groups. The proportion of patients achieving ≥100% of the target dose are presented along with 95% confidence intervals. The proportion of patients on <50% and 50 to <100% were also calculated, χ^2 test was used to compare the proportion of medication classes across SBP groups.

Distribution of SBP was plotted for patients who were not on GDMT defined as fulfilling any of the following; 1) target dose of BB but not target dose of ACEI/ARB/ARNI; 2) target dose of ACEI/ARB/ARNI but not target dose of BB; 3) neither target dose of BB nor target dose of ACEI/ARB/ARNI, so that the percent of patients not receiving guideline-recommended dosing across different SBP thresholds could be described. A sensitivity analysis was conducted using the following SBP cut points (100, 120 and 130 mmHg) to examine the effects on the results. An additional sensitivity analysis excluded those with HR <60 beats per minute, because bradycardia may be a reason for non-intensification of BB.

All analyses were performed using SAS software (version 9.4 SAS Institute, Cary, NC). Analyses were performed independently by the Duke Clinical Research Institute, and the lead author takes responsibility for guiding data analysis and interpretation.

Results:

There were 4,493 patients enrolled across 151 sites in the CHAMP-HF registry between Dec 2015 and Aug 2017. After exclusion of patients ineligible for the registry (n = 42), those with any documented medication-related side effects that could limit use or dosing (n =1105), specific contraindications to ACEI/ARB/ARNI or BB (n = 84), missing SBP (n = 161), and missing demographic information (n= 6), 3,095 patients across 148 sites were included in the final study cohort (Online Figure 1). The median SBP was 120 mmHg [IQR110 - 130] and median diastolic blood pressure (DBP) was 72 mmHg [IQR 64 – 80]. The majority of patients were male (70.6%), older than 64 years (59.6%), white (73.8%) and

had SBP ≥110 mmHg (n = 2421, 78.2%) (Table 1). The median Kansas City Cardiomyopathy Questionnaire-Short Form overall summary score (KCCQ-OS) was 69 (IQR 49 – 85.4) and most patients (84%, n = 2601) had either New York Heart Association (NYHA) II or III symptoms. The median left ventricular ejection fraction (LVEF) was 30% (IQR 23 -36).

Among those with SBP <110, the median SBP /DBP was 100 (IQR 96 – 105)/62 (IQR 60 -69), compared with 124 (IQR 118 – 136)/75 (IQR 70 – 80) among those with SBP ≥110 mmHg. The median heart rate was 73 (IQR 66 – 82) among those with SBP <110 and 72 (IQR 65 -80) among those with SBP≥110 mmHg (Table 1). BB use was lower (81.9% vs 85.6%; p=0.03), ARB use was higher (22.6% vs 14.7 %; p<0.0001), ARNI use was lower (11.6% vs 17.5%; p <0.0001) and ACEI use was similar (41.0% vs 42.4%; p = 0.5) in patients with SBP ≥110 mmHg, compared with those with SBP <110 mmHg. The prevalence of comorbidities and other baseline characteristics by SBP categories are presented in Table 1. The distribution of SBP among patients not receiving target doses had a mean of 120 mmHg and a standard deviation of 17 (Online Figure 2).

Proportion Receiving Target Doses of ACEI/ARB/ARNI or BBs

Among the 3,095 patients who were eligible for ACE/ARB/ARNI and BB, 61% were receiving ACEI/ARB, 12.9% were receiving ARNI, and 82.7% were receiving a BB (Figure 1). The proportion of patients receiving target doses for these medication classes were 10.8% (95% CI 9.7– 1.9) for ACEI/ARB, 2.0% (95% CI 1.5–2.5) for ARNI, and 18.7 % (95% CI 17.3–20.0) for BBs (Table 2). Among those with SBP <110 mmHg and were eligible for both ACEI/ARB/ARNI and BB (n= 674), 6.2 % (95% CI 4.4–8.1), 1.8% (95% CI 0.8–2.8) and 17.5% (95% CI 14.6–20.4), were receiving target doses of ACEI/ARB, ARNI and BBs, respectively. A greater proportion of patients were receiving <50% of target doses than were receiving > 50% (Table 2, Figure 2). Among those with SBP ≥110 mmHg who were eligible for both ACE/ARB/ARNI and BB (n=2421), the proportion of patients receiving target doses were 12.1% (95% CI 10.8–13.4) for ACEI/ARB, 2.0% (95% CI 1.5–2.6) for ARNI, and 19.0% (95% CI 17.4–20.6) for BBs. Similarly, a greater proportion of patients were receiving < 50% than were receiving > 50% of target doses for each drug class despite having SBP ≥110mm Hg. (Table 2, Figure 3).

Finally, among patients who were already prescribed two classes of medications including a BB (i.e an ACEI/ARB/ARNI and a BB, (n= 1,619)), only 8.8% (n= 142) were receiving target doses of both (Table 3, Figure 4). Among those with SBP <110 mmHg, 5.8% (n =22) were receiving target doses of both an ACEI/ARB/ARNI and a BB (Table 3). For those with SBP ≥110 mmHg, 9.7% (n = 120) were receiving target doses of both an ACEI/ARB/ARNI and a BB (Table 3). A sensitivity analysis excluding patients with heart rate < 60 bpm produced qualitatively similar results (Supplemental Tables 2a-c). In an additional sensitivity analysis, the proportion of patients receiving target doses of ACEI/ARB increased slightly with increase in SBP cutoff (11.2%, 13.6%, 17.3% among patients with SBP ≥ 100, ≥ 120, and ≥ 130 mmHg respectively; Supplemental Tables 3a, 4a and 5a). The results were otherwise similar to the primary analysis (Supplemental Tables 3-5).

Discussion:

Translating the benefits of medical therapies that were previously observed in clinical trials to clinical practice partly depends on using therapies in a manner similar to that tested in the clinical trials and endorsed by guidelines. In fact, in an explicit test of the intensity of ACEI dose, the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial found lower rates of mortality and hospitalization with higher vs lower dose lisinopril(7). Similar dose dependent benefit has been demonstrated with angiotensin blockers and beta blockers (8,15). We analyzed a contemporary cohort of patients with HFrEF enrolled in the CHAMP-HF registry because the prescription patterns of dosing intensity according to blood pressure in patients with HFrEF in contemporary US practice is not known. We found an overwhelming majority of patients eligible for either BBs or ACEI/ARB/ARNI were not receiving target doses and that most patients were on <50% of guideline recommended target doses, even after excluding those with medication-specific intolerance or contraindications. Importantly, SBP did not appear to be a barrier to intensifying treatment overall, as marked under treatment was noted in those with a SBP ≥110 mmHg, with an overall similar pattern noticed when we considered SBP ≥120 and SBP≥130 mmHg. Despite a majority of our cohort (52.3%) receiving both a BB and an ACEI/ARB/ARNI, the proportion of patients receiving target doses of both types of medication (beta blockade and angiotensin inhibition) was only slightly higher among those with SBP ≥110 mmHg (9.7%) compared with those having a SBP <110 mmHg (5.8%). Finding that less than 1 in 10 patients in both cohorts were optimally treated with GDMT highlights an important opportunity to intensify foundational HF therapies to potentially further improve morbidity and mortality (9,16).

We used an SBP cutoff of 110 mmHg in our primary analyses because prior analyses utilizing an SBP threshold of 110 showed that while overall risk of death and hospitalizations increase below this threshold in HFrEF, ARB(17), ARNI(18) and BB(19) were associated with reduced mortality and hospitalizations even at SBP < 110 mmHg. We also selected this threshold to reflect a range above which (i) clinicians will likely be more comfortable initiating or intensifying HF medications that affect systemic blood pressure and (ii) further reductions in SBP documented in clinical trials with up-titration were unlikely to result in symptomatic hypotension (17,18). Yet, even with higher SBP levels in sensitivity analyses, the proportion of patients receiving suboptimal medication doses remained high.

Our study adds to the body of evidence showing that despite the dose-response relationship for GDMT with outcomes (20-22), sub-optimal dosing of HF medications remain highly prevalent, and provides new insight that SBP may not be a primary barrier to dosing intensification. Sub-optimal dosing has previously been observed in a population of outpatients with HFrEF(23) and in patients who underwent ICD implantation, an indication predicated upon the use of GDMT at appropriate doses (24). Patient factors (e.g. older age, comorbid lung disease or diabetes, intolerance or contraindications medication cost), and physician factors (e.g. physician knowledge/global self-confidence) have been suggested as potential reasons for suboptimal dosing of HF therapy (25,26). Our study prospectively collected some of these data and excluded patients intolerant of ACEI/ARB/ARNIs and BBs

while further exploring whether blood pressure and heart rate could have potentially precluded the institution or intensification of these heart failure therapies (12,27).

Clinical hypotension is commonly considered at SBP <90 mmHg (28), and if present, may cause clinicians to defer or de-escalate therapy (especially if patients are symptomatic). Moreover, SBP ranges between 90 – 110 mmHg may still generate considerable provider discomfort with respect to intensifying HF medications that reduce SBP. However, an SBP >110 mmHg is not considered hypotension, and we posit that a greater proportion of clinicians should be comfortable instituting or intensifying HF medical therapy at these levels.

While low SBP has been associated with poor prognosis in HFrEF (29-31), angiotensin inhibition and beta-blockade have demonstrated improved outcomes, independent of baseline blood pressure (18,21). Our findings of lower overall use of target doses of BBs and ACEI/ARB/ARNI in those with SBP <110 mmHg may reflect clinician hesitation to up-titrate medical therapy due to the association of low SBP and worse outcomes. However, blood pressure level should not be a significant factor among those with SBP ≥110 mmHg. There is a need for qualitative studies to further refine our understanding of how clinicians use SBP in decision making on intensification of medication therapy in HF. In the interim, more aggressive efforts to ensure appropriate medication dosing such as the creation of EMR or clinic-based performance measures may be needed.

Clinical inertia, may contribute to suboptimal dosing of effective therapies (10). Clinical inertia is a well described concept that refers to the failure to act on a clinically identified problem(32). Although we posited that blood pressure might be a potential factor contributing to clinical inertia related to intensifying HF therapy, it seemed to have at most a modest impact, suggesting that other factors contributed to the under-dosing of HF medications. There is an urgent need for concurrent efforts aimed at availing patients of the best medical therapy while simultaneously investigating factors related to sub-optimal dosing of important HF medications in patients who can tolerate them. Despite the advances in treatment, mortality rates for HFrEF remain high (33,34), and the previously observed improvements in mortality among patients with HF appears to have slowed down over recent decades (35). Given the multiple observations that sub-optimal dosing of critical HF therapy is highly prevalent, and the potential survival benefit associated with optimal dosing of HF therapy(36,37), there is a critical opportunity for developing and promoting strategies aimed at stimulating wide spread adoption of optimal HF treatments, including treating to effective medication doses. Performance measures are one way of stimulating adoption of best medical practices, but current performance measures rely on the presence or absence of use of specific medication classes and not the intensity of treatment(38). Given the evidence that medication dose is important to achieve better outcomes in HFrEF, performance measures should consider evolving to reflect the achievement of appropriate doses.

Limitations:

Our study is a descriptive analysis and was intended to explore a potential rationale for not intensifying HF medications to guideline-recommended doses. As a cross-sectional analysis,

we cannot comment on changes in treatment over time (in subsequent visits), although patients had been under the care of their providers prior to enrollment in CHAMP-HF. We did not include other evidence-based mediations such as mineralocorticoid antagonists (MRA), which also reduce blood pressure. However, MRA use is typically recommended after optimization of ACEI/ARB and BBs. Although we included a diverse cohort from 151 practices, these findings may not be generalizable to other US patients and practices. While careful attention was paid to adjudicating intolerances, there may have been patients with undocumented intolerances or preferences precluding the use of BBs or ACEI/ARB/ARNI. Further, we assessed SBP at one point in time. It is unknown if SBP was labile, whether physicians relied upon home SBP measurements, or if patients had reported symptoms potentially associated with symptomatic hypotension that may have led to a reduction or inability to up-titrate BB or ACEI/ARB therapies at the time of the clinical visit. ARNI use was low in our study and this is likely a reflection of the recent approval of this drug class. There was a high representation of white male participants in our study. Whether our results apply to other demographic groups remain unclear. Finally, the study was not designed to identify why optimal medication doses were not used.

Conclusion:

In a contemporary cohort of patients with HFrEF, we found that over 90% of patients determined to be eligible for BB and ACEI/ARB/ARNI, and with SBP ≥110 mmHg were not receiving target doses of therapies that have been previously shown to reduce morbidity and mortality in HFrEF. Further efforts, which may include intensive education through the electronic medical record, defined protocols, improvements in transition of patients between providers, creation of dosing-based performance measures, patient education and other strategies are needed to support the use of more effective, guideline-recommended doses of HF medications in patients with HFrEF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ACEI	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor- neprilysin inhibitor
BB	beta-blocker

CHAMP-HF	CHAnge the Management of Patients with Heart Failure
GDMT	guideline directed medical therapy
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
TIA	transient ischemic attack
TD	target dose

References

1. Benjamin EJ, Blaha MJ, Chiuve SE et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017;135:e146–e603. [PubMed: 28122885]
2. Sacks CA, Jarcho JA, Curfman GD. Paradigm Shifts in Heart-Failure Therapy – A Timeline. New England Journal of Medicine 2014;371:989–991. [PubMed: 25184412]
3. Colucci WS, Packer M, Bristow MR et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation 1996;94:2800–6. [PubMed: 8941105]
4. Packer M, Fowler MB, Roecker EB et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194–9. [PubMed: 12390947]
5. Yancy CW, Jessup M, Bozkurt B et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Journal of cardiac failure 2017;23:628–651. [PubMed: 28461259]
6. Packer M, McMurray JJ, Desai AS et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. Circulation 2015;131:54–61. [PubMed: 25403646]
7. Packer M, Poole-Wilson PA, Armstrong PW et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation 1999;100:2312–8. [PubMed: 10587334]
8. Bristow MR, Gilbert EM, Abraham WT et al. Carvedilol Produces Dose-Related Improvements in Left Ventricular Function and Survival in Subjects With Chronic Heart Failure. Circulation 1996;94:2807–2816. [PubMed: 8941106]
9. Fiuzat M, Wojdyla D, Kitzman D et al. Relationship of beta-blocker dose with outcomes in ambulatory heart failure patients with systolic dysfunction: results from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial. Journal of the American College of Cardiology 2012;60:208–15. [PubMed: 22560018]
10. Bhatt AS, DeVore AD, DeWald TA, Swedberg K, Mentz RJ. Achieving a Maximally Tolerated beta-Blocker Dose in Heart Failure Patients: Is There Room for Improvement? Journal of the American College of Cardiology 2017;69:2542–2550. [PubMed: 28521892]
11. Heywood JT, Fonarow GC, Yancy CW et al. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. Circulation Heart failure 2010;3:596–605. [PubMed: 20634483]
12. Parwani P, Ryan J. Heart failure patients with low blood pressure: how should we manage neurohormonal blocking drugs? Circulation Heart failure 2012;5:819. [PubMed: 23170021]
13. DeVore AD, Thomas L, Albert NM et al. Change the management of patients with heart failure: Rationale and design of the CHAMP-HF registry. Am Heart J 2017;189:177–183. [PubMed: 28625374]

14. Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240–327. [PubMed: 23741058]
15. Konstam MA, Neaton JD, Dickstein K et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009;374:1840–8. [PubMed: 19922995]
16. Ouwerkerk W, Voors AA, Anker SD et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J 2017.
17. Anand IS, Rector TS, Kuskowski M, Thomas S, Holwerda NJ, Cohn JN. Effect of baseline and changes in systolic blood pressure over time on the effectiveness of valsartan in the Valsartan Heart Failure Trial. Circulation Heart failure 2008;1:34–42. [PubMed: 19808268]
18. Bohm M, Young R, Jhund PS et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. Eur Heart J 2017;38:1132–1143. [PubMed: 28158398]
19. Montero-Perez-Barquero M, Flather M, Roughton M et al. Influence of systolic blood pressure on clinical outcomes in elderly heart failure patients treated with nebivolol: data from the SENIORS trial. European journal of heart failure 2014;16:1009–15. [PubMed: 25044535]
20. Wikstrand J, Hjalmarson A, Waagstein F et al. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure: analysis of the experience in metoprolol CR/XL randomized intervention trial in chronic heart failure (MERIT-HF). Journal of the American College of Cardiology 2002;40:491–8. [PubMed: 12142116]
21. Metra M, Torp-Pedersen C, Swedberg K et al. Influence of heart rate, blood pressure, and beta-blocker dose on outcome and the differences in outcome between carvedilol and metoprolol tartrate in patients with chronic heart failure: results from the COMET trial. Eur Heart J 2005;26:2259–68. [PubMed: 16040619]
22. Vardeny O, Claggett B, Packer M et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. European journal of heart failure 2016;18:1228–1234. [PubMed: 27283779]
23. Greene SJ, Butler J, Albert NM et al. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. Journal of the American College of Cardiology 2018;72:351–366. [PubMed: 30025570]
24. Miller AL, Wang Y, Curtis J, Masoudi FA, Buxton AE, Wang TY. Optimal medical therapy use among patients receiving implantable cardioverter/defibrillators: insights from the National Cardiovascular Data Registry. Archives of internal medicine 2012;172:64–7. [PubMed: 22082711]
25. Komajda M, Follath F, Swedberg K et al. The EuroHeart Failure Survey programmea survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003;24:464–74. [PubMed: 12633547]
26. Fuat A, Hungin APS, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. BMJ (Clinical research ed) 2003;326:196.
27. Gorelik O, Feldman L, Cohen N. Heart failure and orthostatic hypotension. Heart failure reviews 2016;21:529–38. [PubMed: 26880254]
28. Patel PA, Heizer G, O'Connor CM et al. Hypotension during hospitalization for acute heart failure is independently associated with 30-day mortality: findings from ASCENDHF. Circulation Heart failure 2014;7:918–25. [PubMed: 25281655]
29. Ambrosy AP, Vaduganathan M, Mentz RJ et al. Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. Am Heart J 2013;165:216–25. [PubMed: 23351825]
30. Gheorghiade M, Vaduganathan M, Ambrosy A et al. Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure. Heart failure reviews 2013;18:107–22. [PubMed: 22581217]

31. Komajda M, Bohm M, Borer JS et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. European journal of heart failure 2014;16:810–6. [PubMed: 24961493]

32. Phillips LS, Branch WT, Jr, Cook CB, et al. CLinical inertia. Annals of internal medicine 2001;135:825–834. [PubMed: 11694107]

33. Curtis LH, Greiner MA, Hammill BG et al. Early and long-term outcomes of heart failure in elderly persons, 2001-2005. Archives of internal medicine 2008;168:2481–8. [PubMed: 19064833]

34. Hummel SL, Pauli NP, Krumholz HM et al. Thirty-day outcomes in Medicare patients with heart failure at heart transplant centers. Circulation Heart failure 2010;3:244–52. [PubMed: 20061519]

35. Tsao CW, Lyass A, Enserro D et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart failure 2018;6:678–685. [PubMed: 30007560]

36. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential Mortality Reduction With Optimal Implementation of Angiotensin Receptor Neprilysin Inhibitor Therapy in Heart Failure. JAMA cardiology 2016;1:714–7. [PubMed: 27437874]

37. Fonarow GC, Yancy CW, Hernandez AF, Peterson ED, Spertus JA, Heidenreich PA. Potential impact of optimal implementation of evidence-based heart failure therapies on mortality. Am Heart J 2011;161:1024–30.e3. [PubMed: 21641346]

38. Bonow RO, Ganiats TG, Beam CT et al. ACCF/AHA/AMA-PCPI 2011 Performance Measures for Adults With Heart Failure. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures and the American Medical Association–Physician Consortium for Performance Improvement 2012;125:2382–2401.

PERSPECTIVES

Competency in Medical Knowledge: In a contemporary cohort of patients with HFrEF, utilization of target doses of ACEI/ARB/ARNI or BB was low among patients eligible for these therapies (at most 20%), even with SBP ≥130. The majority of patients were not treated or were on <50% of recommended doses. No therapy was used at guideline recommended doses in more than 1 in 5 patients.

Translational Outlook: Further studies into strategies that improve intensification of foundational evidence-based medical therapies in HFrEF are needed.

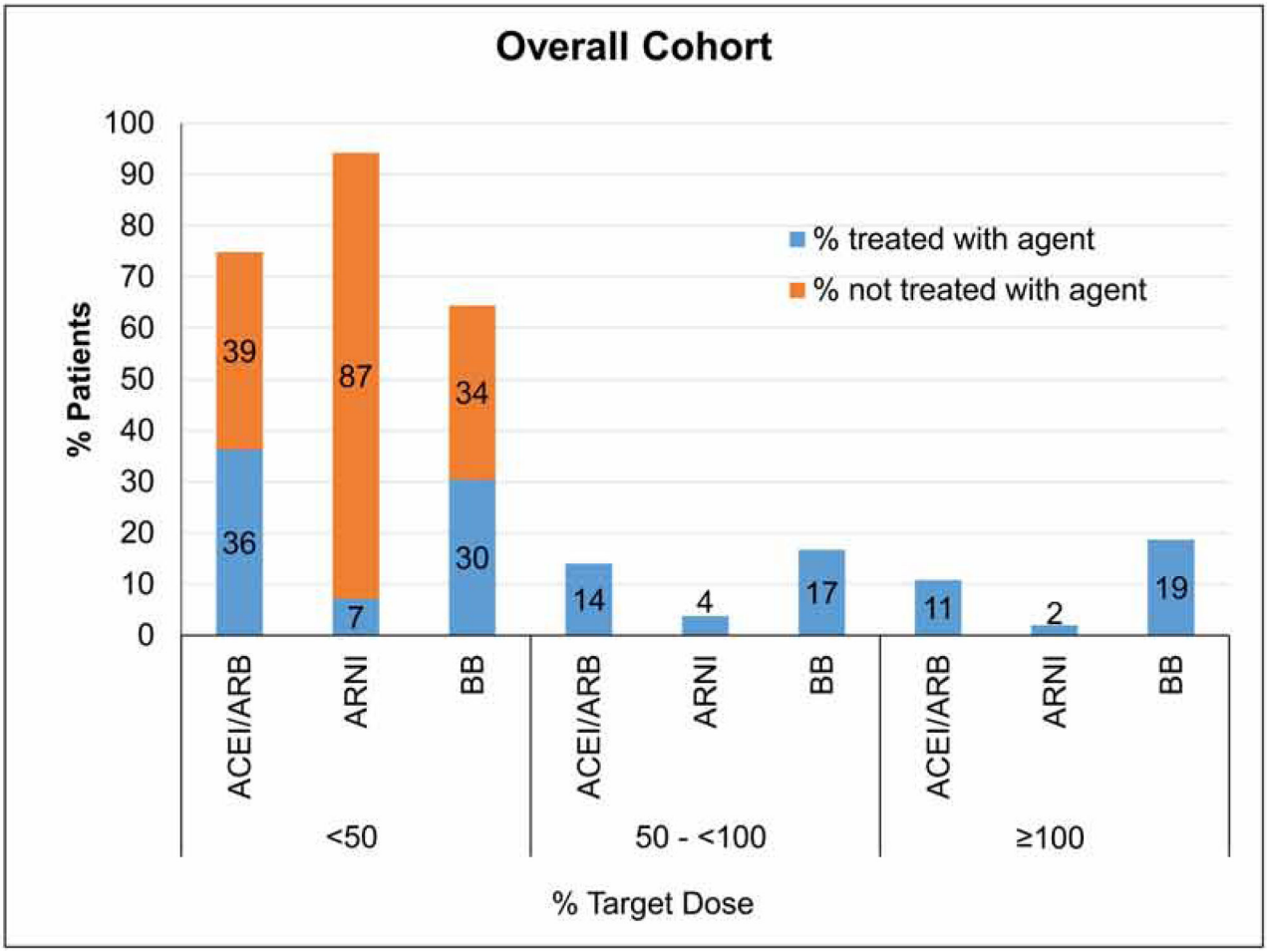

Figure 1: Distribution of percent target doses for each medication class in the overall cohort.

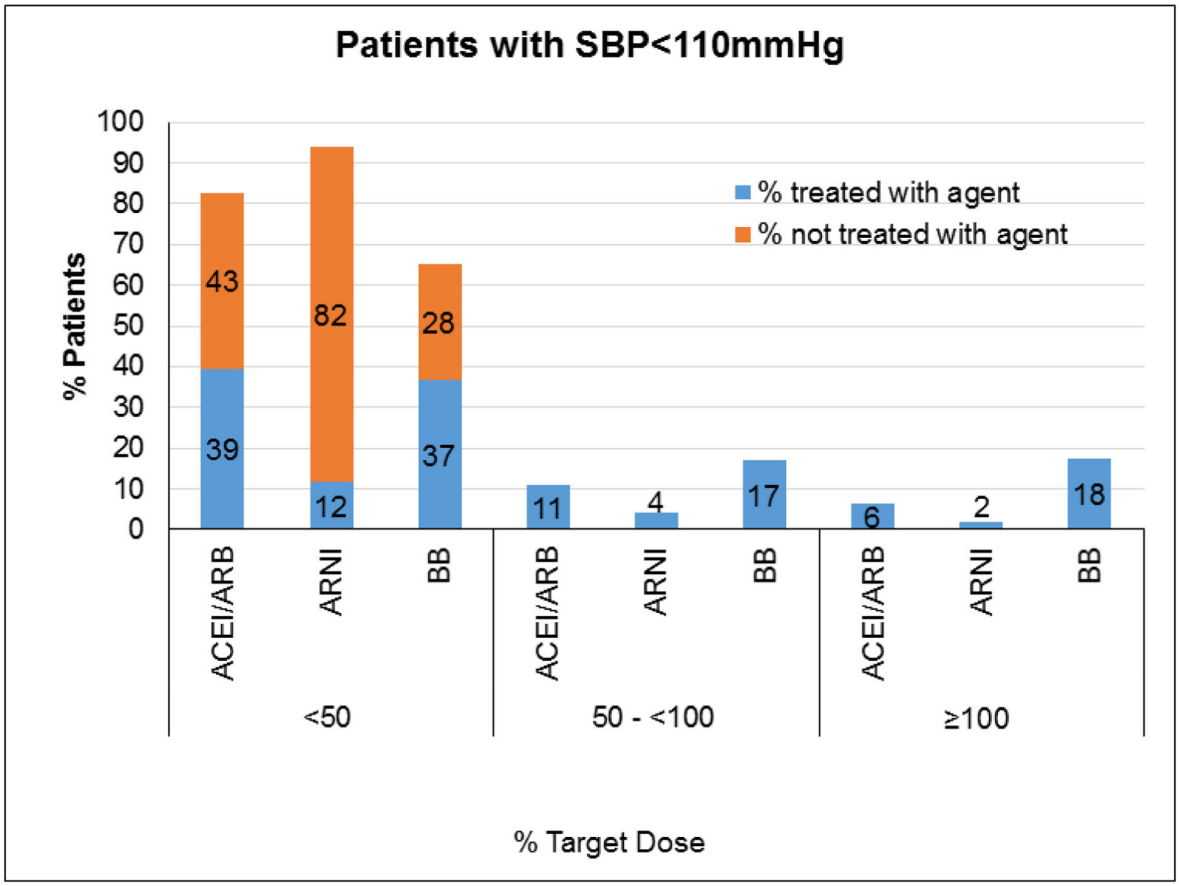

Figure 2: Distribution of percent target doses for each medication class among patients with SBP< 110mmHg.

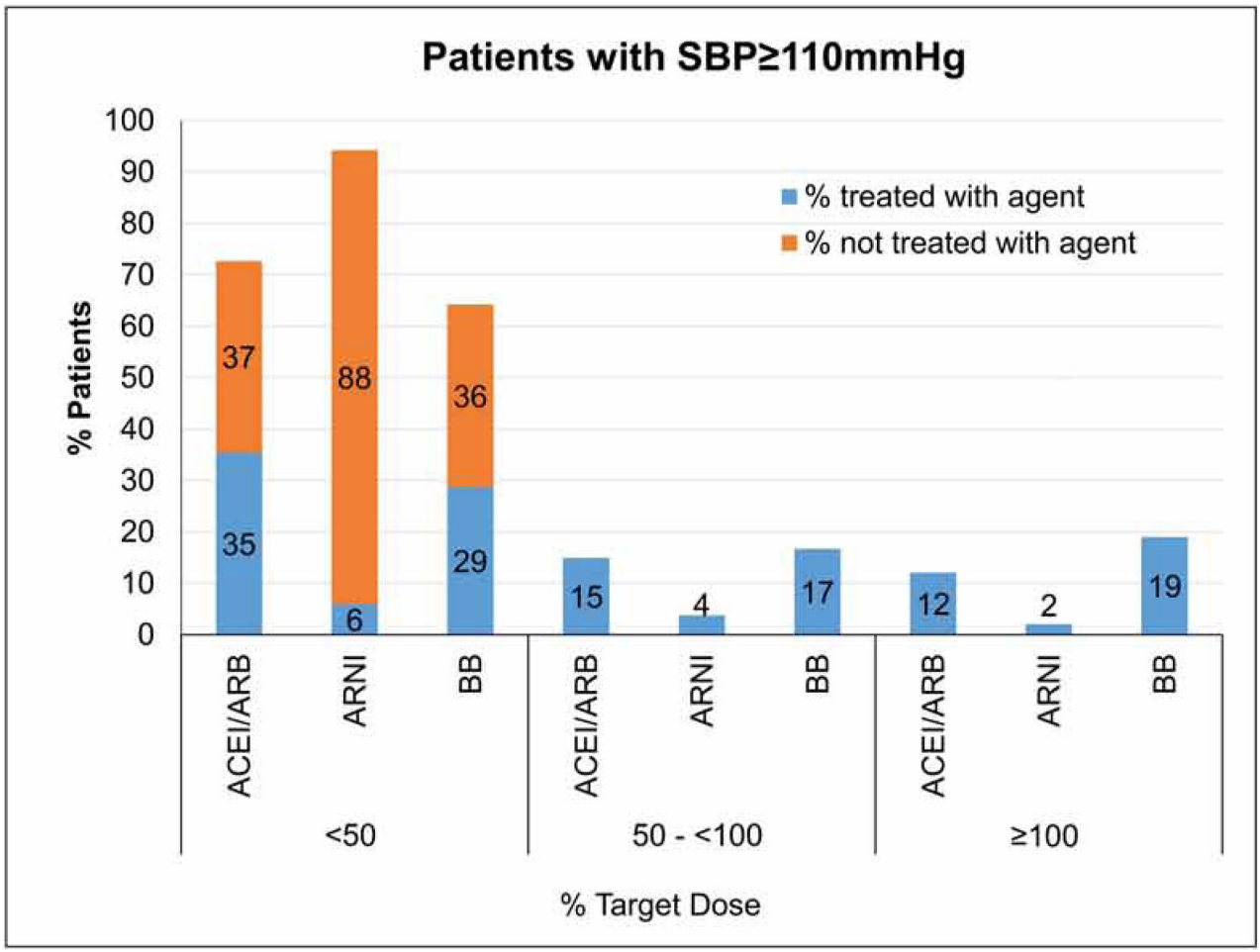

Figure 3: Distribution of percent target doses for each medication class among patients with SBP≥110mmHg.

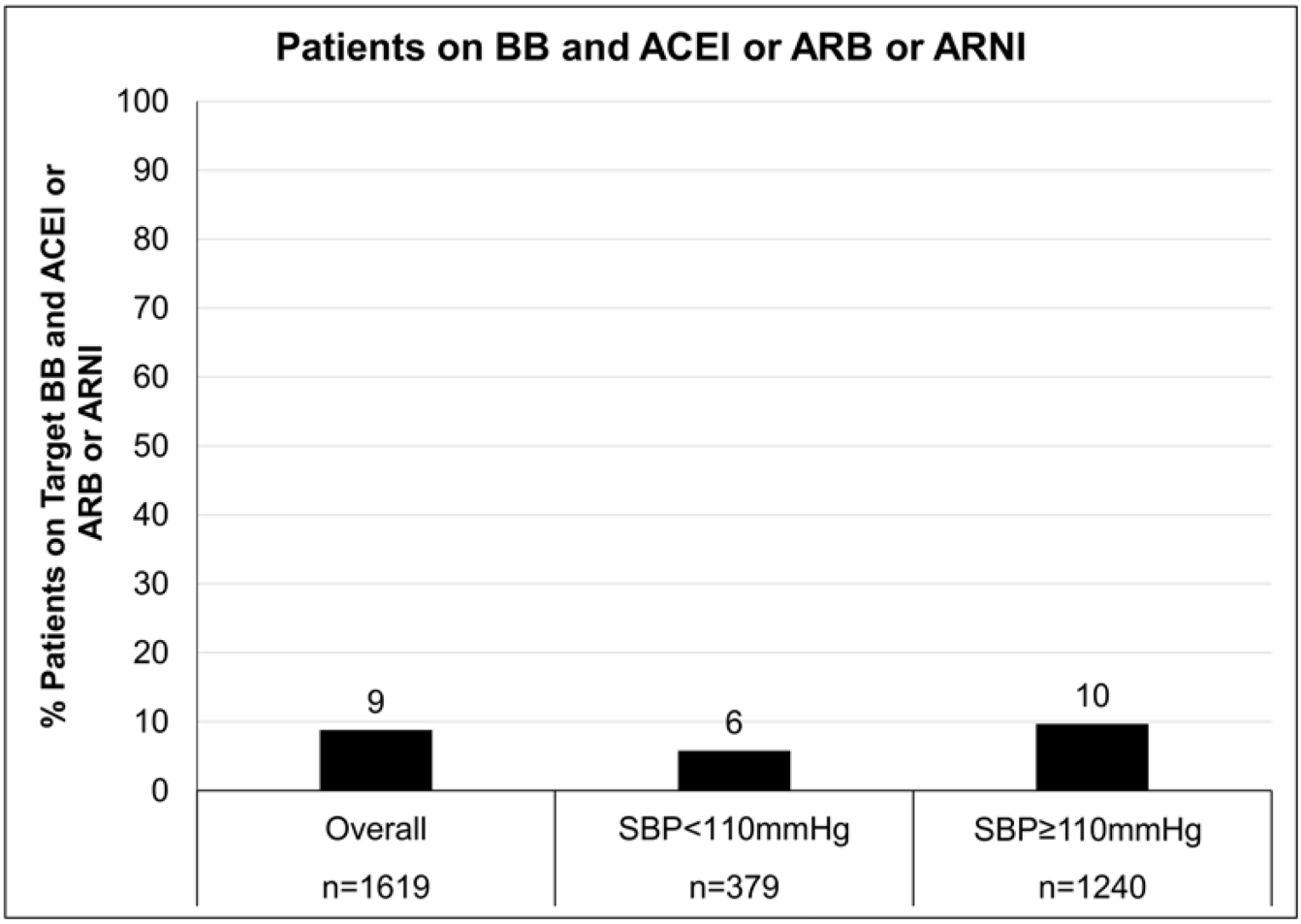

Figure 4: Distribution of percent of patients receiving target doses of BB and ACEI or ARB or ARNI among patients receiving BB and ACEI or ARB or ARNI.

Table 1.

Demographic and Clinical Characteristics of the Study Population overall and by SBP Categories

		Systolic Blood Pressure	
	Overall N=3095	**<110 mmHg N=674**	**≥110 mmHg N=2421**
Demographics			
Age (y)			
Median (Q1-Q3)	68.0 (59.0-75.0)	66.0 (57.0-74.0)	68.0 (59.0-76.0)
<40	100 (3.2%)	35 (5.2%)	65 (2.7%)
40-64	1,150 (37.2%)	275 (40.8%)	875 (36.1%)
65-80	1,448 (46.8%)	288 (42.7%)	1,160 (47.9%)
80+	397 (12.8%)	76 (11.3%)	321 (13.3%)
Gender			
Male	2,184 (70.6%)	477 (70.8%)	1,707 (70.5%)
Female	911 (29.4%)	197 (29.2%)	714 (29.5%)
Race			
White	2,283 (73.8%)	513 (76.1%)	1,770 (73.1%)
Black	519 (16.8%)	111 (16.5%)	408 (16.9%)
Other/unknown	293 (9.5%)	50 (7.4%)	243 (10.0%)
Medical history			
Chronic renal insufficiency	552 (17.8%)	127 (18.8%)	425 (17.6%)
COPD	943 (30.5%)	196 (29.1%)	747 (30.9%)
Dementia	69 (2.2%)	11 (1.6%)	58 (2.4%)
Diabetes mellitus	1,285 (41.5%)	251 (37.2%)	1,034 (42.7%)
Hepatic dysfunction	64 (2.1%)	19 (2.8%)	45 (1.9%)
Peripheral artery disease	422 (13.6%)	75 (11.1%)	347 (14.3%)
Stroke/TIA	325 (10.5%)	69 (10.2%)	256 (10.6%)
Ischemic heart disease	1,195 (38.6%)	258 (38.3%)	937 (38.7%)
Myocardial infarction	1,039 (33.6%)	244 (36.2%)	795 (32.8%)
Hypertrophic cardiomyopathy	214 (6.9%)	22 (3.3%)	192 (7.9%)
Restrictive cardiomyopathy	43 (1.4%)	9 (1.3%)	34 (1.4%)
Vital signs			
Systolic Blood Pressure (mmHg)	120 (110 – 130)	100 (96 – 105)	124 (118 – 136)
Diastolic blood pressure (mmHg)	72 (64-80)	62 (60-69)	75 (70-80)
Heart rate (bpm)	72 (66-81)	73 (66-82)	72 (65-80)
Clinical measures/Labs			
NYHA Classification			
I	339 (11.0%)	64 (9.5%)	275 (11.4%)
II	1,787 (57.7%)	366 (54.3%)	1,421 (58.7%)
III	814 (26.3%)	206 (30.6%)	608 (25.1%)
IV	69 (2.2%)	20 (3.0%)	49 (2.0%)
LVEF (%))	30 (22-36)	28 (20-33)	32 (25-37)

		Systolic Blood Pressure	
	Overall N=3095	**<110 mmHg N=674**	**≥110 mmHg N=2421**
<20	324 (10.5%)	131 (19.4%)	193 (8.0%)
20-25	722 (23.3%)	174 (25.8%)	548 (22.6%)
26-35	1,257 (40.6%)	255 (37.8%)	1,002 (41.4%)
36-40	772 (24.9%)	106 (15.7%)	666 (27.5%)
eGFR (mL/min/1.73 m2)	60 (50-70)	60 (47-61)	60 (51-73)
<30	94 (3.0%)	31 (4.6%)	63 (2.6%)
30-45	259 (8.4%)	67 (9.9%)	192 (7.9%)
45-60	425 (13.7%)	116 (17.2%)	309 (12.8%)
>=60	1,205 (38.9%)	239 (35.5%)	966 (39.9%)
Medication at enrollment			
ACEI	1,279 (41.3%)	286 (42.4%)	993 (41.0%)
ARB	646 (20.9%)	99 (14.7%)	547 (22.6%)
MRA	1,006 (32.5%)	298 (44.2%)	708 (29.2%)
Beta blocker	2,560 (82.7%)	577 (85.6%)	1,983 (81.9%)
ARNI	400 (12.9%)	118 (17.5%)	282 (11.6%)
Quality of life assessment			
KCCQ12	68.8 (49.0-85.4)	65.4 (45.8-84.0)	69.3 (50.0-85.4)

Data are median (interquartile range) or n (%). ACEI = angiotensin converting enzyme inhibitor ; ARNI =angiotensin receptor- neprilysin inhibitor ;ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; KCCQ = Kansas City Cardiomyopathy Questionnaire ; LVEF= left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; TIA = transient ischemic attack

Table 2:

Baseline medication in the overall cohort (n = 3095), among patients with SBP<110 mmHg (N=674), and SBP≥110 mmHg (N=2421)

	Treated (n)	Not Treated (n)	<50% TD (n)	50% to <100% TD (n)	≥100% TD (n)	%TD (95% CI)
Overall Cohort						
ACEI/ARB	1901	1194	1122	434	334	10.8 (9.7, 11.9)
ARNI	400	2695	220	118	61	2.0 (1.48, 2.46)
Beta Blocker	2043	1052	942	518	578	18.7 (17.3, 20.0)
SBP<110 mmHg						
ACEI/ARB	382	292	265	73	42	6.2 (4.41, 8.06)
ARNI	118	556	78	28	12	1.8 (0.78, 2.78)
Beta Blocker	483	191	248	114	118	17.5 (14.6, 20.4)
SBP ≥100 mmHg						
ACEI/ARB	1519	902	857	361	292	12.1 (10.8, 13.4)
ARNI	282	2139	142	90	49	2.0 (1.46, 2.58)
Beta-Blocker	1560	861	694	404	460	19.0 (17.4, 20.6)

ACEI = angiotensin converting enzyme inhibitor; ARNI =angiotensin receptor- neprilysin inhibitor; ARB = angiotensin receptor blocker; TD = Target dose.

%TD = n(≥100%TD)/n(Treated)

Table 3.

Summary of patients receiving target BB and ACEI/ARB/ARNI doses among those on both a BB and one of ACEI/ARB/ARNI (N=1619)

Target BB	**Target ACEI/ARB/ARNI SBP<110 mmHg**			**Target ACEI/ARB/ARNI SBP≥110 mmHg**		
	No	Yes	Total	No	Yes	Total
No	263 69.4%	16 4.2%	279 73.6%	755 60.9%	116 9.4%	871 70.2%
Yes	78 20.6%	22 5.8%	100 26.4%	249 20.1%	120 9.7%	369 29.8%
Total	341 90.0%	38 10.0%	379 100%	1004 81.0%	236 19.0%	1240 100%

ACEI = angiotensin converting enzyme inhibitor; ARNI =angiotensin receptor- neprilysin inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker