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Tolerability of Angiotensin Receptor Neprilysin Inhibitor (ARNI) with Two Classes of Beta-Blockers: A Real-world Retrospective Study in a Tertiary Hospital

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ABSTRACT

Objective: Our study compares the use of ARNI plus Carvedilol or ARNI plus Bisoprolol in real-world settings to assess suboptimal ARNI use due to hypotension.

Methods: A respective single-center study was performed in a tertiary hospital in the Riyadh region from 2017 to 2021. We studied individuals diagnosed with HFrEF who have started using ARNI drugs. First patients who were on ARNI plus Bisoprolol, while the second group included patients who were on ARNI plus Carvedilol. A descriptive analysis was conducted, and a chi-square test was used to assess the differences between categorical variables and outcomes. The statistically significant p-value was less than 0.05.

Results: Our study included 151 participants, of which 96 received the medication Bisoprolol and 55 received the medication Carvedilol. In the two groups, the average patient age is about 55 years old. In the two therapy groups, there were no significant differences in age or gender ($p > 0.05$). Also, both the bisoprolol and the carvedilol groups had mean systolic blood pressure values of about 126 mmHg. The suboptimal ARNI use confirmed that none of the beta-blockers was superior to the other in terms of suboptimal ARNI use due to hypotension, hyperkalemia, and elevated serum creatinine ($p > 0.05$). Finally, the difference between the bisoprolol and carvedilol groups regarding the discontinuation, the down-titration, and the maintenance of initial or medium doses of ARNI use was non-significant for all three events.

Conclusion: The utilization of either bisoprolol or carvedilol as the beta blocker of choice in therapeutic regimens of HFrEF with sacubitril/valsartan, as they provide the same level of ARNI tolerability.

Keywords: Heart Failure; ARNI; Beta-Blockers; Bisoprolol; Carvedilol

Abbreviations: HF: Heart Failure; ACEIs: Angiotensin-Converting Enzyme Inhibitors

Introduction

Heart failure (HF) is a serious medical problem in Saudi Arabia, where people's quality of life is still significantly impacted despite the use of advanced therapies [1]. Thirty years ago, angiotensin-converting enzyme inhibitors (ACEIs) had been demonstrated to reduce overall HF mortality by 16–40% [2,3]. Angiotensin-receptor blockers (ARBs) have similar effects as ACEIs but work by blocking the AT1 receptor and interfering with the action of angiotensin II. In 2001, the Val-HeFT trial established the use of ARB therapy for patients diagnosed with HF [4]. Three beta-blockers for HF, namely bisoprolol, carvedilol, and sustained-release metoprolol, can block adrenergic

activation and lead to a substantial reduction in mortality [5-7]. The mineralocorticoid receptor antagonist (MRAs) spironolactone has been proven to reduce mortality by 30% among patients already receiving ACEIs in the RALES trial [8]. Also, the EMPHASIS-HF trial in 2011 justified and expanded the utilization of MRA eplerenone in patients with mildly symptomatic HF [9]. The cornerstones of modern HF therapy are these neurohumoral antagonists. As a result, after the PARADIGM-HF trial's release in 2014, there was a significant paradigm change in HF therapy [10]. The trial showed that, compared to enalapril, a novel strategy to HF medication called angiotensin-receptor and neprilysin inhibition (ARNI) by the combination of sacubitril and valsartan resulted in a 20% reduction in cardiovascular mortality and a 16% reduction in all-cause mortality.

The American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) recently updated evidence-based recommendations for the management of HF, according to this study [11,12]. Both guidelines provided class I, level of evidence B recommendation to replace ACEIs by sacubitril/valsartan in patients with chronic symptomatic HF with reduced ejection fraction (HFrEF) despite optimal treatment [13]. In HFrEF, β-blockers have a well-known record of reducing mortality and hospitalization [14]. Carvedilol therapy is a multiple action non-selective β-adrenergic receptor blocker that also induces α1-adrenergic receptor blockade and has been shown to improve the state of HF patients in several large-scale trials [7]. However, the most common adverse clinical effects of carvedilol include dizziness and hypotension, which appear to be mainly related to an α1 blockade effect (vasodilation). On the other hand, bisoprolol, a highly selective β1-adrenergic receptor blocker, has also been found to be effective for HF patients in multiple studies [15]. Patients with heart failure and a lower ejection fraction (HFrEF) frequently have low blood pressure. Although spontaneous hypotension is a risk indicator for HFrEF, there is only weak evidence linking hypotension experienced during heart failure (HF) drug titration to prognosis. In clinical trials, around 10-15% of patients with heart failure (HF) reported having low blood pressure (BP), even though this percentage is substantially greater in everyday clinical practice [2,7,10].

Low BP in HFrEF may have multiple origins, such as low cardiac function, hypovolemia, treatment-related vasodilatation, and altered vasoreactivity related to comorbidities. On the background of several landmark trials, a totally well-established arsenal of medications for the treatment of HFrEF exists. Therefore, clinical practice guidelines strongly articulate recommendations for the initiation and titration of these therapies to target doses. In daily clinical practice, dose adjustment of HFrEF drugs relies on signs and symptoms of HF, BP, and heart rate, biological parameters (mainly creatinine, serum potassium, hemoglobin, and natriuretic peptides), or imaging parameters [11,12,16-18]. Low blood pressure (90 mmHg) is the commonly used measure of low blood pressure in HF patients since it has been consistently highlighted as an indicator of a bad prognosis in cases of acute HF. Target dosages of medications for HFrEF may be difficult due to dose-related declines in BP since clinicians are reluctant to further titrate therapies [12]. Low BP has been observed to frequently restrict the usage and up-titration of some life-saving medications in HFrEF and can lead to stopping these medications [19,20]. Yet, when compared to patients with greater BP, HFrEF patients with low BP levels may potentially benefit from these medications [21,22]. The approved ARNI is available in three doses that include one that was not tested in the HF trial; the target dose of valsartan/sacubitril used in the trial was 97/103 mg twice daily [23].

Theoretically, the use of Carvedilol with ARNI makes the patient more susceptible to hypotension, which limits the successful titration of ARNI and increases the incidence of suboptimal ARNI use. To the best of our knowledge, the suboptimal due to hypotension with the use of two different classes of β-blocker has not been compared or studied yet. Therefore, the aim of our study is to assess suboptimal ARNI use due to hypotension between the use of ARNI plus Carvedilol or ARNI plus Bisoprolol in real world settings.

Method

Study Design

A single-center, retrospective observational cohort study was conducted at the Security Forces Hospital Program in Riyadh from January 2017 to June 2021.

Study Population

Our target population is patients diagnosed with HFrEF who have started using ARNI drugs. To achieve our outcomes, we divided the patients into two groups in our study. The first group was made up of patients who were on ARNI plus Bisoprolol, while the second group included patients who were on ARNI plus Carvedilol.

Inclusion and Exclusion Criteria

In our study, we included patients ages 18 and older diagnosed with HF with a reported LVEF less than 40% by echocardiography test and using either carvedilol or bisoprolol and started on ARNI. On the other hand, patients who lost follow-up or were on any anti-hypertensive medication that was not one of the guidelines-directed medical therapies were excluded from our study [11].

Data Collection

Data collection from the patient's medical records was used to gather baseline demographic data, including age, sex, LVEF, blood pressure, serum potassium, and creatinine. It also included administered beta-blocker dose and administered ARNI dose. Also, variables like BP, LVEF, beta blocker and ARNI doses, serum potassium, and serum creatinine levels were assessed after the start of ARNI and for up to six months after the start.

Outcomes

The primary outcome is to assess the suboptimal ARNI use due to hypotension between the use of ARNI with Carvedilol and ARNI plus Bisoprolol. On the other hand, the secondary outcome, compares the suboptimal ARNI use between the use of ARNI plus Carvedilol and ARNI plus Bisoprolol due to hyperkalemia or elevated serum creatinine. We also compared how these two groups differed in terms of heart failure with improved ejection fraction (HFimpEF) [24].

Definition of ARNI Use

In our study, the criteria of suboptimal ARNI use involves discontinuation of ARNI, down-titration of ARNI dose, or maintaining the initial or medium ARNI doses [25]. Also, the definition of reasons for suboptimal ARNI use is hypotension, determined as the systolic blood pressure being less than 100 mm Hg, hyperkalemia reported to be more than 5.5 mmol/liter for the potassium level, and elevated serum creatinine by more than 30% [10].

Statistical Analysis

A descriptive analysis of the baseline characteristics of the individuals was applied. The median and standard deviation were used for the continuous variables, while percentages and frequencies were used for the categorical variables. The chi-square test was used to assess the differences between categorical variables and outcomes. The cutoff values were p< 0.05, which indicate statistically significant results. The Statistical Package for Social Science (SPSS) version 25 was used to analyze the collected data.

Results

In our study, 151 patients were included; 96 of them received the bisoprolol medication, and 55 received the carvedilol medication. In the bisoprolol group, the mean patient age was 56 years, and 74% of the patients were men, while the mean patient age in the carvedilol group was 54 years, and 63.6% of the patients were men. Age and gender did not significantly differ between the two treatment groups, according to our findings (p > 0.05). The mean systolic blood pressure in the bisoprolol group was 127.97 mmHg, whereas it was 125.31 mmHg in the carvedilol group, which did not statistically differ from one another (p = 0.317). There was no significant different between the bisoprolol group's mean serum creatinine level of 89.61 mg/dl and the carvedilol group's mean serum creatinine level of 91.29 mg/dl (p = 0.732). Furthermore, the mean potassium level was 4.31 mmol/liter in the bisoprolol group and 4.37 mmol/liter in the carvedilol group, with no significant difference between both groups (p = 0.490). Finally, there was no statistically significant difference between the bisoprolol group's baseline LVEF of 28.11% and the carvedilol group's baseline LVEF of 26.55% (p = 0.258). (Table 1) represented the characteristics of the patients in our study. The suboptimal ARNI use confirmed that none of the beta-blockers was superior to the other in terms of suboptimal ARNI use due to hypotension (p=0.515). In addition, the suboptimal ARNI use confirmed that none of the beta-blockers was superior to the other in terms of suboptimal ARNI use due to hyperkalemia (p=0.929) and elevated serum creatinine (p=0.914).

Table 1: Baseline Characteristics of the Patients.

	Bisoprolol (N = 96)	Carvedilol (N = 55)	P value*
Age (years)	56.13 ± 13.074	54.29 ± 14.584	0.428
Gender Male (%) Female (%)	71 (74%) 25 (26%)	35 (63.6%) 20 (36.4%)	0.199
Systolic blood pressure (mm Hg)	127.97±15.393	125.31±16.103	0.317
Serum creatinine (mg/dl)	89.61±31.184	91.29±24.268	0.732
Potassium level (mmol/liter)	4.313±0.4897	4.369±0.4710	0.490
Baseline Left ventricular ejection fraction (%)	28.11 %	26.55 %	0.258

Note: p-value < 0.05

There was no significant different between the bisoprolol and carvedilol groups regarding the improvement in EF being greater than 40% at a 6-month interval (p=0.527). Furthermore, the difference between the bisoprolol and carvedilol groups regarding the discontinuation, the down-titration, and the maintenance of initial or medium doses of ARNI use was non-significant for all three events (p> 0.05). Finally, the target dose of a beta blocker at the end of six months did not significantly differ between the two groups (p=0.767) which is shown in (Table 2).

Table 2: Outcomes of ARNI Plus either Bisoprolol or Carvedilol in Heart Failure Patients.

Event	Bisoprolol (N = 96)	Carvedilol (N = 55)	P – value*
Suboptimal ARNI Use Due to Hypotension			
Suboptimal ARNI use due to hypotension with systolic blood pressure <100 mm Hg.	42 (43.8%)	21 (40.4%)	0.515
Suboptimal ARNI Use Due to Other Reasons			
Suboptimal ARNI use due to hyperkalemia with potassium level of >5.5 mmol/liter.	7 (7.3%)	4 (7.7%)	0.929
Suboptimal ARNI use due to Elevated serum creatinine by more than 30%.	14 (14.6%)	8 (15.4%)	0.914
Efficacy			
HFimpEF: Improvement in EF to be more than 40% through six months follow up.	19 (19.8%)	8 (14.5%)	0.527
Type of Suboptimal ARNI Use			
Discontinuation	12 (12.5%)	6 (10.9%)	0.241
Down-titration	3 (3.1%)	1 (1.8%)	0.142
Maintained initial or medium doses	13 (13.5%)	3 (5.5%)	0.103

Note: p-value < 0.05

Discussion

According to our study, individuals with HFrEF who started using ARNI after taking Bisoprolol or Carvedilol experienced similar suboptimal ARNI use due to hypotension and other reasons. Patients with HFrEF who are in NYHA functional classes II to III have showed a decrease in mortality and hospitalization rates in several randomized trials of particular beta blockers, such as carvedilol, metoprolol succinate, and bisoprolol [5,26-29]. A meta-analysis has shown that beta blockers are beneficial for reducing mortality after one and two years [30]. A randomized double-blind experiment (PARADIGM-HF) also demonstrated sacubitril/superiority valsartan's to enalapril in the treatment of HFrEF [10]. A study has reported that patients who receive beta blockers and ARNI at 50% to 99% of their target dose (TD) have a better prognosis than those who only receive one of these medications at more than 100% of the TD [31]. It has also been shown in another study that the use of beta-blockers, renin-angiotensin system inhibitors, and angiotensin receptor neprilysin inhibitors is related with a lower risk of mortality and morbidity in patients with heart failure [32]. Nevertheless, hypotension is one of the major preventive measures in achieving optimal pharmacologic therapy doses for HFrEF and may be exacerbated or induced by concomitant ARNI and beta-blocker therapy. Additionally, compared to enalapril, sacubitril/valsartan has been seen to have a greater risk of symptomatic hypotension [10].

In our study, among the three main causes of suboptimal ARNI use identified in the current research, hypotension was the most frequent reason, with an average of 42.1% between the two study groups. Although 43.8% of the patients in the bisoprolol group and 40.4% of those in the carvedilol group received suboptimal ARNI use due to hypotension, the difference between the beta-blocker arms was negligible. Our results suggest that neither of the two beta blockers investigated is statistically inferior to the other in terms of the incidence of suboptimal ARNI use due to hypotension. The result is in accordance with other studies comparing bisoprolol and carvedilol in patients with heart failure [33-35]. The HEAAL trial, has pointed out that the clinical benefit of a high-dose ARB comes with an increased risk of kidney impairment, hyperkalemia, and hypotension [36]. However, lower rates of hyperkalemia and renal impairment have been reported with ARNIs [10]. In our study, elevated serum creatinine and hyperkalemia accounted for an average of 15% and 7.5% of suboptimal ARNI use, respectively. However, the results suggest that none of the two beta blockers investigated is inferior to the other in terms of the incidence of suboptimal ARNI use due to hyperkalemia or elevation in serum creatinine. After six months, 14.5% of patients in the carvedilol group and 19.8% of patients receiving bisoprolol had improved ejection fraction (EF > 40%), however this difference was not statistically significant.

The result of the current work is in line with a network meta-analysis of 21 trials with a focus on atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol, where β-blockers illustrated obvious mortality benefits in comparison with standard treatment or placebo after 12 months, which showed the improvements in left ventricular ejection fraction were similar irrespective of the individual study drug [37]. Moreover, we concluded that regarding discontinuation, down-titration, or maintained initial or medium doses of ARNI, both beta blocker classes indicated unremarkable differences. Overall, our results comparing the two different beta blockers depict that there is no class superiority between bisoprolol and carvedilol concerning our primary outcomes. Conversely,

investigators have opined that due to carvedilol's vasodilatory effect, it could exert more clinically vigorous outcomes in HFrEF in contrast to selective beta inhibitors, including bisoprolol and metoprolol. The COMET (Carvedilol or Metoprolol European Trial) study, a large randomized controlled trial comparing carvedilol and metoprolol, found that carvedilol extended survival compared to metoprolol in patients with chronic heart failure [38]. Meanwhile, this study had two major limitations. First, metoprolol tartrate, which has not been proven to reduce mortality in HF and is not advised by guidelines, was compared to carvedilol. Second, lower than recommended doses of metoprolol were provided compared to the full indicated dose of carvedilol. The mortality benefits of carvedilol and bisoprolol were comparable in a multicenter cohort study carried out in Korea, which supports our interpretation [39].

Limitations

It is important to understand this study in light of its limitations. First, the small number of patients that were enrolled in the study is its primary limitation. Second, during the trial period, only 20.8% of the patients were on the target dose of beta blockers. Finally, most of the sample was made up of men, which might make it difficult to generalize the findings to include both genders. Therefore, it is essential that a bigger, randomized clinical trial be performed with a larger sample size.

Conclusion

Our findings support the use of either bisoprolol or carvedilol as the beta blocker of choice in therapeutic regimens of HFrEF with sacubitril/valsartan, as they provide the same level of ARNI tolerability.

References

1. Aljefree N, Ahmed F (2015) Prevalence of cardiovascular disease and associated risk factors among adult population in the Gulf region: A systematic review. Advances in Public Health 2015.
2. Swedberg K, Kjekshus J (1988) Effects of enalapril on mortality in severe congestive heart failure: Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The American journal of cardiology 62(2): 60A-66A.
3. S Yusuf, B Pitt, CE Davis, WB Hood Jr, JN Cohn (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. New England Journal of Medicine 325(5): 293-302.
4. Cohn JN, Tognoni G (2001) A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. New England Journal of Medicine 345(23): 1667-1675.
5. Investigators C I (1999) The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomised trial. The Lancet 353(9146): 9-13.
6. Group M HS (1999) Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in-congestive heart failure (MERIT-HF). The Lancet 353(9169): 2001-2007.
7. Packer M, Fowler MB, Roecker EB (2002) Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 106(17): 2194-2199.
8. Pitt B, Zannad F, Remme WJ (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine 341(10): 709-717.
9. Zannad F, McMurray JJ, Krum H (2011) Eplerenone in patients with systolic heart failure and mild symptoms. New England Journal of Medicine 364(1): 11-21.
10. McMurray JJ, Packer M, Desai AS (2014) Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 371: 993-1004.
11. Yancy CW, Jessup M, Bozkurt B (2017) 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 the American College of Cardiology 70(6): 776-803.
12. Ponikowski P, Voors AA, Anker SD (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiologia Polska (Polish Heart Journal) 74(10): 1037-1147.
13. Senni M, McMurray JJ, Wachter R (2016) Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. European journal of heart failure 18(9): 1193-1202.
14. Vardeny O, Claggett B, Kachadourian J (2018) Incidence, predictors, and outcomes associated with hypotensive episodes among heart failure patients receiving sacubitril/valsartan or enalapril: the PARADIGM-HF Trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). Circulation: Heart Failure 11(4): e004745.
15. Metra M, Nodari S, Cas LD (2001) β-Blockade in Heart Failure. American Journal of Cardiovascular Drugs 1(1): 3-14.
16. Girerd N, Seronde MF, Coiro S (2018) Integrative assessment of congestion in heart failure throughout the patient journey. JACC: Heart Failure 6(4): 273-285.
17. Aronson D, Burger AJ (2004) Relation between pulse pressure and survival in patients with decompensated heart failure. The American journal of cardiology 93(6): 785-788.
18. Jackson CE, Castagno D, Maggioni AP (2015) Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: Results from the MAGGIC individual patient meta-analysis. European heart journal 36(18): 1106-1114.
19. Komajda M, Schöpe J, Wagenpfeil S (2019) Physicians' guideline adherence is associated with long-term heart failure mortality in outpatients with heart failure with reduced ejection fraction: The QUALIFY international registry. European Journal of Heart Failure 21(7): 921-929.
20. Komajda M, Anker SD, Cowie MR (2016) Physicians' adherence to guideline-recommended medications in heart failure with reduced ejection fraction: Data from the QUALIFY global survey. European journal of heart failure 18(5): 514-522.
21. Rouleau JL, Roecker EB, Tendera M (2004) Influence of pretreatment systolic blood pressure on the effect of carvedilol in patients with severe chronic heart failure: the Carvedilol Prospective Randomized Cumulative

Survival (COPERNICUS) study. Journal of the American College of Cardiology 43(8): 1423-1429.

22. Böhm M, Young R, Jhund PS (2017) 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. European heart journal 38(15): 1132-1143.
23. Yancy CW, Januzzi JL, Allen LA (2018) 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: Answers to 10 pivotal issues about heart failure with reduced ejection fraction: A report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. Journal of the American College of Cardiology 71(2): 201-230.
24. Heidenreich PA, Bozkurt B, Aguilar D, Larry AA, Joni JB, et al. (2022) 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 79(17): e263-e421.
25. Pogge EK, Davis LE (2018) Evaluating the Safety and Tolerability of Sacubitril/Valsartan for HFrEF Managed Within a Pharmacist Clinic. Am J Cardiovasc Drugs 18(2): 143-151.
26. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, et al. (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. New England Journal of Medicine 334(21): 1349-1355.
27. Fowler MB, Vera Llonch M, Oster G, MR Bristow, JN Cohn, et al. (2001) Influence of carvedilol on hospitalizations in heart failure: Incidence, resource utilization and costs. Journal of the American College of Cardiology 37(6): 1692-1699.
28. Packer M, Coats AJ, Fowler MB, Andrew JSC, Hugo AK, et al. (2001) Effect of carvedilol on survival in severe chronic heart failure. New England Journal of Medicine 344(22): 1651-1658.
29. CR M (1999) Effect of metoprolol CR/XL in chronic heart failure. Lancet 353(9169): 2001-2007.
30. Brophy JM, Joseph L, Rouleau JL (2001) β-Blockers in congestive heart failure: a Bayesian meta-analysis. Annals of internal medicine 134(7): 550-560.
31. D Amario D, Rodolico D, Rosano GM, Ulf D, Filippo C, et al. (2022) Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry. European Journal of Heart Failure 24(5): 871-884.
32. Stolfo D, Lindberg F, Lund L, G Sinagra, U Dahlstrom, et al. (2022) Association between use of renin-angiotensin system inhibitors/angiotensin receptor neprilysin inhibitors and beta-blockers and outcome in real-world heart failure and mildly reduced ejection fraction. European Heart Journal 43(Supplement_2): ehac544. 847.
33. Lainscak M, Podbregar M, Kovacic D, Rozman J, von Haehling S, et al. (2011) Differences between bisoprolol and carvedilol in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized trial. Respiratory medicine 105: S44-S49.
34. Düngen HD, Apostolović S, Inkrot S, Elvis T, Agnieszka T, et al. (2011) Titration to target dose of bisoprolol *vs.* carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. European journal of heart failure 13(6): 670-680.
35. Edelmann F, Musial Bright L, Gelbrich G, Tobias T, Sara R, et al. (2016) CIBIS-ELD Investigators and Project Multicenter Trials in the Competence Network Heart Failure. Tolerability and feasibility of beta-blocker titration in HFpEF versus HFrEF: insights from the CIBIS-ELD trial JACC Heart Fail 4(2): 140-149.
36. Kiernan MS, Wentworth D, Francis G, Felipe AM, Kenneth D, et al. (2012) Predicting adverse events during angiotensin receptor blocker treatment in heart failure: Results from the HEAAL trial. European journal of heart failure 14(12): 1401-1409.
37. Chatterjee S, Biondi Zoccai G, Abbate A, Fabrizio D, Davide C, et al. (2013) Benefits of β blockers in patients with heart failure and reduced ejection fraction: Network meta-analysis. Bmj 346.
38. Poole Wilson PA, Swedberg K, Cleland JG, Andrea DL, Peter H, et al. (2003) 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. The Lancet 362(9377): 7-13.
39. Choi KH, Lee GY, Choi JO, Hae YL, Eun-Seok Jeon, et al. (2019) The mortality benefit of carvedilol versus bisoprolol in patients with heart failure with reduced ejection fraction. The Korean journal of internal medicine 34(5): 1030.

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