Utilization of guideline-directed medical therapy in patients with de novo heart failure with reduced ejection fraction: A Veterans Affairs study

Mohamad Khattab¹, Purvi Parwani³, Mubasher Abbas³, Huzair Ali¹, Pedro M. Lozano¹,², Udho Thadani¹,², Tarun W. Dasari¹

¹University of Oklahoma Health Sciences Center, Oklahoma City, OK, ²Veterans Affairs Medical Center, Oklahoma City, OK, ³Loma Linda University International Heart Institute, Loma Linda, CA, United States

ABSTRACT

Background: The utilization of guideline-directed medical therapy (GDMT) significantly reduces morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF). Previous studies have documented the underutilization of GDMT in HFrEF. The present study aimed to determine reasons for underutilization and achievement of target doses of GDMT in patients with de novo diagnosis of HFrEF.

Methods: Patients presenting with de novo HFrEF at the Veterans Affairs Medical Center were included. Baseline demographic, clinical, and echocardiographic data were collected. The utilization of target doses of GDMT was assessed at the time of discharge and 1-, 3-, 6-, and 12-month follow-up.

Results: Of the 95 patients who met the criteria for de novo HFrEF, 48 were included in the final analysis. Dose titration of either beta-blocker or angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) was attempted in 20 patients (42%) at 1 month, 21 patients (44%) at 3 months, 13 patients (27%) at 6 months, and 14 patients (29%) at 12 months. Nine (19%) patients were on a target dose of beta-blockers and three (6%) patients were on a target dose of an ACEi/ARB at 12 months. The most common reasons for underutilization were patient-level factors, such as hypotension, acute kidney injury/hyperkalemia, and patient noncompliance.

Conclusions: Utilization and achievement of target doses of GDMT were suboptimal among patients discharged with de novo HFrEF during a 1-year follow-up. Although patient factors may limit the up-titration of therapies, concerted efforts are needed to support primary care physicians in improving adherence to target doses of GDMT in patients with HFrEF.

Keywords: Cardiomyopathy, guideline-directed medical therapy, heart failure

Introduction

Heart failure (HF) is a leading cause of morbidity and mortality in the United States.¹²³ The American Heart Association estimates that, between 2013 and 2016, 6.2 million adults had HF; this number has increased from 5.7 million between 2009 and 2012.² It is projected that the prevalence of HF will increase even further, with experts predicting a 46% increase in prevalence between 2012 and 2030.⁴⁻⁷⁻¹⁰ Medical therapy for heart failure with reduced ejection fraction (HFrEF) has led to significant reductions in morbidity and mortality.¹³⁻¹⁵ Consensus treatment guidelines make strong recommendations for the utilization of guideline-directed medical therapy (GDMT), which includes angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs) and beta-blockers in patients with symptomatic heart failure and an EF <40%.¹⁶⁻¹⁹ Utilization of GDMT has been reported, but there are little data specifically

Address for correspondence: Dr. Tarun W. Dasari, Cardiovascular Section, Department of Medicine, 800 SL Young Blvd, COM 5400, University of Oklahoma HSC, Oklahoma City, Oklahoma - 73104, United States. E-mail: tarun-dasari@ouhsc.edu

Received: 31-01-2020 Revised: 13-03-2020 Accepted: 24-03-2020 Published: 30-06-2020

Access this article online

Quick Response Code: Website: www.jfmpc.com DOI: 10.4103/jfmpc.jfmpc_174_20

How to cite this article: Khattab M, Parwani P, Abbas M, Ali H, Lozano PM, Thadani U, et al. Utilization of guideline-directed medical therapy in patients with de novo heart failure with reduced ejection fraction: A Veterans Affairs study. J Family Med Prim Care 2020;9:3065-9.
addressing the reasons for the underutilization of GDMT in de novo HFrEF. The present study sought to determine the utilization and achievement of target doses of GDMT in patients with de novo HFrEF and to identify reasons for underutilization.

**Methods**

We conducted a retrospective cohort study at the Veterans Affairs Medical Center. Ethical clearance for this study was approved by the institutional review board at our institution. Inclusion criteria were adults older than age 18 and admission to the inpatient cardiology service with a primary diagnosis of de novo heart failure with a left ventricular ejection fraction of <40%. Exclusion criteria were known diagnosis of HFrEF, an EF >40%, hypertensive urgency/emergency, a life expectancy of less than 1 year, concomitant acute illnesses such as sepsis/acute surgical pathologies, and acute neurological events (stroke/hemorrhage).

Demographics, comorbid conditions, and echocardiographic parameters were recorded at baseline for each participant. The utilization of GDMT was assessed at the time of discharge and during follow-up 1, 3, 6, and 12 months later. Utilization of target doses of beta-blockers (metoprolol succinate 200 mg daily, carvedilol 25–37.5 mg twice daily, and bisoprolol 10 mg daily) and ACEi (Lisinopril 20–40 mg daily, enalapril 10–20 mg twice daily, quinapril 20 mg twice daily, captopril 50 mg three times daily)/ARBs (losartan 100–150 mg daily, candesartan 32 mg daily, and valsartan 160 mg twice daily) was obtained. Since the study dates spanned from 2011–2015, we did not have information on the utilization of angiotensin receptor blockers/neprilysin inhibitors. Reasons for holding therapy or avoiding up-titration of therapy were obtained by review of clinician documentation.

**Results**

Ninety-five patients with newly diagnosed HFrEF were screened, of which 48 were included in our final analysis [see Figure 1]. Baseline characteristics are presented in Table 1. All patients were males (as the study was conducted at a Veterans Affairs hospital); the mean age was 63 ± 6 years, 79% were Caucasian, and 69% had nonischemic cardiomyopathy. Reasons for underutilization of target doses of GDMT are listed in Table 2. The most common reasons were hypotension, acute kidney injury, and patient noncompliance.

**Baseline**

At baseline, 44 (92%) patients were discharged on beta-blockers and 38 (79%) were discharged on an ACEi/ARB, regardless of dose. Seven (15%) patients were on a target dose of a beta-blocker and seven (15%) patients were on a target dose of an ACEi/ARB.

**One month**

A clinical follow-up appointment with a healthcare provider occurred in 37 (77%) patients at 1 month. Dose titration of either beta-blocker or ACEi/ARB was attempted in 20 (42%) patients at 1 month. Six (13%) patients were on a target dose of a beta-blocker and three (6%) patients were on a target dose of an ACEi/ARB.

**Three months**

A clinical follow-up appointment with a healthcare provider occurred in 25 (52%) patients at 3 months. Dose titration of either beta-blocker or ACEi/ARB was attempted in 21 (44%) patients at 3 ± 1 month. Six (13%) patients were on a target dose of a beta-blocker and two (4%) patients were on a target dose of an ACEi/ARB.

![Figure 1: Screening log for selection of de novo heart failure patients](image)

| Table 1: Baseline demographics and characteristics |
|--------------------------------------------------|
| Characteristic | Number (percentage) |
|----------------|---------------------|
| Male           | 48 (100%)           |
| Mean Age       | 63±6 years          |
| Ethnicity      |                     |
| White          | 38 (79%)            |
| African American| 9 (19%)             |
| Other race     | 1 (2%)              |
| Hypertension   | 42 (88%)            |
| Diabetes Mellitus| 22 (46%)           |
| Coronary Artery Disease | 19 (40%)  |
| Non-ischemic Cardiomyopathy | 33 (69%) |
| Chronic Kidney Disease | 2 (4%)      |
| Chronic Obstructive Pulmonary Disease | 13 (27%) |
| Medication use at baseline: | | |
| Beta Blocker   | 24 (50%)            |
| *ACEi          | 18 (38%)            |
| ^ARB           | 1 (2%)              |
| *ACEi or ^ARB  | 19 (40%)            |
| Spironolactone | 11 (23%)            |
| Hydralazine/Isosorbide Dinitrate | 4 (8%)     |
| Loop Diuretics | 20 (42%)            |
| Digoxin        | 14 (29%)            |
| Aspirin        | 20 (42%)            |

*Denotes angiotensin-converting enzyme inhibitor ^Denotes angiotensin receptor blocker
Six months
A clinical follow-up appointment with a healthcare provider occurred in 26 (54%) patients at 6 months. Dose titration of either beta-blocker or ACEi/ARB was attempted in 13 (27%) patients at 6 ± 1 month. Thirteen (27%) patients were on a target dose of a beta-blocker and four (8%) patients were on a target dose of an ACEi/ARB.

One year
A clinical follow-up appointment with a healthcare provider occurred in 28 (58%) patients at 12 ± 1 month. Dose titration of either beta-blocker or ACEi/ARB was attempted in 14 (29%) patients at 12 months. Nine (19%) patients were on a target dose of a beta-blocker and three (6%) patients were on a target dose of an ACEi/ARB.

The utilization of spironolactone was 23% at baseline, with no attempt to up-titrate the dosage during the follow-up visits. The utilization of isosorbide dinitrate/hydralazine was 8% at baseline, with no attempts to up-titrate the dosage during the follow-up visits. Reasons for failure to up-titrate spironolactone or isosorbide dinitrate/hydralazine were not documented. Rates of the utilization of target doses of ACEi/ARB and beta-blocker over time are depicted in Figure 2.

Discussion
The current study demonstrates that despite a meaningful utilization of basic heart failure drug therapies, such as beta-blockers and renin-angiotensin system blockers, the achievement of target doses, and attempts to up-titrate to target doses of GDMT were subpar. In one study, the prevalence of GDMT use for patients with HFrEF and diabetes mellitus is reported to be relatively high: ACEiARBs (86%) and beta-blockers (83%). Another study comparing patients in the US, with high and low-income Asian countries, identified that rates of utilization of ACEi/ARBs were 77%, 76%, and 69%, respectively; beta-blocker utilization rates were 91%, 87%, and 69%, respectively. However, both of these studies failed to assess the doses of these medications, and the latter study suggests that the utilization of GDMT in HFrEF patients is lower in Asia than in the US, although the difference between rates of utilization of target doses in these regions remains unclear. Our study is unique in that it captures data on the prescription patterns for de novo HFrEF and provides granular data, spread over the first 12 months after diagnosis. It also demonstrates that attempts to up-titrate dosing and documentation of attempts may also be subpar within the Veterans Affairs System, specifically amongst primary care physicians, who assume the majority of the care for these patients after an initial post-hospital visit with cardiovascular physicians.

Heart failure is associated with increased morbidity and mortality. Despite the availability and utilization of GDMT, the mortality rates continue to be unacceptably high in the US and elsewhere. While the reasons for these rates are multifold, underutilization of adequate doses of GDMT is partly to blame. To derive maximal benefits, guidelines recommend that evidence-based

| Table 2: Reasons for underutilization of guideline-directed medical therapy |
|------------------|------------------|------------------|------------------|------------------|
|                  | Number (percentage) at 1 month | Number (percentage) at 3 months | Number (percentage) at 6 months | Number (percentage) at 12 months |
| No documentation | 14 (29%)           | 13 (27%)           | 29 (60%)           | 33 (69%)           |
| Hypotension      | 19 (40%)           | 22 (46%)           | 11 (23%)           | 5 (10%)            |
| Bradycardia      | 3 (6%)             | 0 (0%)             | 0 (0%)             | 0 (0%)             |
| Acute Kidney Injury/Hyperkalemia | 4 (8%) | 0 (0%) | 5 (10%) | 5 (10%) |
| Patient Noncompliance | 4 (8%) | 11 (23%) | 0 (0%) | 0 (0%) |
| Drug Allergy     | 4 (8%)             | 2 (4%)             | 0 (0%)             | 0 (0%)             |
| Other nonspecific Reason | 0 (0%) | 0 (0%) | 3 (6%) | 5 (10%) |

Figure 2: Rates of the utilization of target doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) and beta-blockers (BB) over time
Utilization and achievement of target doses of GDMT, specifically beta-blockers, ACEi/ARBs, spironolactone, and isosorbide dinitrate/hydralazine, was suboptimal among patients discharged with newly diagnosed HFrEF, during a 1-year follow-up. Although patient factors, most commonly hypotension and bradycardia, may limit the up-titration of therapies in some patients, concerted efforts are needed to further improve adherence to target doses of GDMT in patients with HFrEF. Given the majority of follow-up visits beyond an initial posthospital visit by a cardiovascular physician are performed by primary care providers, it is prudent to refocus our efforts on improving their ability to achieve target doses of basic heart failure therapies.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Bytici I, Bajraktari G. Mortality in heart failure patients. Anatol J Cardiol 2015;15:63-8.
2. Bui A, Horwich T, Fonarow G. Epidemiology and risk profile of heart failure. Nat Rev Cardiol 2011;8:30-41.
3. Benjamin E, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2020 update: A report from the American Heart Association. Circulation 2020;139:e57-e526.
4. Fang N, Jiang M, Fan Y. Ideal cardiovascular health metrics and risk of cardiovascular disease or mortality: A meta-analysis. Int J Cardiol 2016;214:279-83.
5. Fowler MB. Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: Carvedilol in severe heart failure. Am J Cardiol 2004;93:358-98.
6. Fagerberg B. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 1999;353:293-302.
7. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
8. 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.
9. Komajda M, Lapuerta P, Hermans N, Gonzalez-Juanatey JR, van Veldhuisen DJ, Erdmann E, et al. Adherence to guidelines is a predictor of outcome in chronic heart failure: The MAHLER survey. Eur Heart J 2005;26:1653-9.
10. Yancy WC, 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. J Am Coll Cardiol 2013;61:e147-239.
11. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr,
Colvin MM, 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. J Am Coll Cardiol 2017;70:776-803.

12. Bhatt AS, Luo N, Solomon N, Pagidipati NJ, Ambrosio G, Green JB, et al. International variation in characteristics and clinical outcomes of patients with type 2 diabetes and heart failure: Insights from TECOS. Am Heart J 2019;218:57-65.

13. Arnold, SV Yap J, Lam CSP, et al. Management of patients with diabetes and heart failure with reduced ejection fraction: an international comparison. Diabetes Obes Metab 2018;21:261-6.

14. Yancy CW, Januzzi JL Jr, Allen LA, Butler J, Davis LL, Fonarow GC, et al. 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. J Am Coll Cardiol 2018;71:201-30.

15. Peri-Okonny PA, Mi X, Khariton Y, Patel KK, Thomas L, Fonarow GC, et al. Target doses of heart failure medical therapy and blood pressure: Insights from the CHAMP-HF registry. JACC Heart Fail 2019;7:350-8.

16. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction: CHAMP-HF registry. J Am Coll Cardiol 2019;73:2365-83.

17. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, et al. Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. J Am Coll Cardiol 2018;72:351-66.

18. Smeets M, Van Roy S, Aertgeerts B, Vermandere M, Vaes B. Improving care for heart failure patients in primary care, GPs’ perceptions: A qualitative evidence synthesis. BMJ Open 2016;6:e013459.

19. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: Primary results of the registry to improve the use of evidence-based heart failure therapies in the outpatient setting (IMPROVE HF). Circulation 2010;122:585-96.

20. Morton G, Masters J, Cowburn PJ. Multidisciplinary team approach to heart failure management. Heart 2018;104:1376-82.