A Retrospective Study of the Treatment Outcome of Drug Therapies used in Heart Failure Patients with Associated Co-morbidities in a Tertiary Care Hospital

HARISH THANUSUBRAMANIAN[1], MEENA KUMARI KAMAL KISHORE[2], RANJAN SHETTY[3], MOHAN BABU AMBERKAR[4]

ABSTRACT

Introduction: Heart failure is one of the most common heart problems seen in the Indian population. There are various drugs used to prevent further progression of the disease. In India, there are few studies in relation to treatment outcome in a tertiary care hospital.

Aim: To study the treatment outcome of drug therapies used in heart failure patients with associated co-morbidities in a tertiary care hospital.

Materials and Methods: This was an observational study conducted on 250 patients with heart failure. Details collected using the proforma were demography (age, gender); medical history; medication history for heart failure patients on admission and discharge; ejection fraction; median length of stay in hospital; number of readmissions & in-hospital mortality.

Results: One hundred and twenty eight patients categorized into LVSD group (ejection fraction <40%) and 122 patients in PSF group (ejection fraction > 40%). Medical history of coronary artery disease (54%) was significantly higher in LVSD group (p<0.05) and anaemia (19%) was significantly higher in PSF group (p<0.05). On admission, inotropes (30%), digoxin (59%) and statins (54%) were prescribed more in LVSD patients (p<0.05) while calcium channel blockers (20%) were prescribed more in PSF group (p<0.05). At discharge, patients with LVSD were receiving ACE inhibitors (51%), beta blockers (30%), digoxin (67%) and statins (59%) (p<0.05) while calcium channel blockers (20%) was prescribed more in PSF group. The median length of stay was slightly higher in patients with PSF (7 days) as compared to LVSD (6 days). In-hospital mortality was lower in patients with PSF (6%) than patients with LVSD (20%). The percentage of readmissions within one month was slightly higher in patients with PSF (15%) compared to LVSD (14%).

Conclusion: Length of stay in hospital was 6-7 days in heart failure patients. In hospital mortality in LVSD patients (20%) was higher compared to PSF patients (6%). A 15% heart failure patient were readmitted within 1month of discharge.

INTRODUCTION

Heart Failure (HF) is a clinical syndrome characterized by an inherited or acquired abnormality of cardiac structure and/or function. They also show clinical symptoms (dyspnea and fatigue) and signs (oedema and rales) that lead to frequent hospitalizations, poor quality of life and shortened life expectancy [1]. Some studies reveal that hospitalized patients with preserved ejection fraction have more chance of developing acute HF than with low ejection fraction [2].

In USA, around 30% to 40% of patients die from HF within 1 year of diagnosis [1]. HF has a high 5-year mortality that is equal to that of many cancers. Risk factors such as ischemic heart disease, hypertension, smoking, obesity and diabetes increase the risk of HF and have poor outcomes [3]. In 2001, Mendez and Cowie stated that there were no population-based HF studies in developing countries and thus making it difficult to estimate global prevalence. In 1949, Vakil studied the epidemiology of HF in 1281 hospitalized patients in India. The primary causes for HF were hypertension-coronary (31%), rheumatic heart disease (29%), syphilis (12%), and pulmonary problems (9%) [4]. In India, there is less data regarding the exact prevalence and incidence of HF. However, with higher risk for cardiovascular diseases and ageing population, HF is likely to be more in comparison to the western population. As a result there is a need of having HF registries in the secondary, tertiary care centers and at the national level [5].

The data from the National Health and Nutrition Epidemiologic Survey (NHANES) 2009 showed that coronary heart disease (60% of cases) had the largest impact on HF development [6]. Some studies reveal that coronary artery disease, hypertension and diabetes mellitus are equally responsible for chronic heart failure [7]. A cross-sectional cohort in elderly patients showed the involvement of various co-morbidities like anaemia, hypertension, diabetes mellitus etc., [8]. As multiple co-morbidities are associated with HF, the drugs used to treat them are important.

The study, which was conducted in Kasturba hospital, Manipal, focused on the treatment outcome of drugs used when patients were admitted as in-patient, after discharge and follow-up at one month. One month post discharge review was important as previous studies have revealed that new diagnosed cases of HF are at high risk of hospital readmission within one month [9]. This study also included treatment outcome of co-morbidities associated with heart failure.

MATERIALS AND METHODS

The study was carried out after obtaining Institutional Ethics Committee (IEC) clearance (letter no. IEC 516/2013). A retrospective analysis of 250 HF patients diagnosed between 01 January 2010 and 30 September 2013 was done. Patients of both sexes above 18 years of age, diagnosed as HF (based on Framingham criteria) and patients with associated co-morbidities were included in the study. Patients with end organ disease of kidney, liver and lung developed before developing HF and loss of follow-up at one month were excluded. All the patients were divided into two groups (Left Ventricular Systolic Dysfunction LVSD

and Preserved Systolic Function PSF) based on ejection fraction. LVSD is ejection fraction less than equal to 40% whereas PSF is ejection fraction more than 40%. The following details were collected using the proforma which included demography (age, gender), medical history of the patients and medication history for HF patients on admission & discharge, ejection fraction, median length of stay in hospital, number of readmissions and in-hospital mortality.

STATISTICAL ANALYSIS

Statistical analysis was analysed using SPSS software version 16.0. Parametric data was analysed by independent t-test and repeated measures Analysis of Variance (ANOVA) while non-parametric data was analysed by Chi-square test for strength of association. Mann-Whitney U test was used for skewed data. Outcome measures were analysed using logistic regression.

RESULTS

Among the 250 patients mortality was seen in 32 patients during inpatient management while remaining 218 patients recovered after treatment and was discharged. Among the 218 patients 31 patients had readmission to the hospital within one month (due to heart failure symptoms) while remaining 187 patients came for follow-up at the end of one month. Among 250 HF patients, 92 patients had hypertension (diagnosed cases) and 91 patients had type 2 diabetes mellitus (diagnosed cases) as major co-morbidities.

As shown in [Table/Fig-1], there were 128 patients categorized into LVSD group (ejection fraction <40%) and 122 patients in PSF group (ejection fraction > 40%). Mean age of both the groups was comparable and was not statistically significant. Male patients showed higher preponderance than females in both the groups and there was statistical significant difference between the two groups with p-value < 0.05. Medical history of coronary artery disease was significantly higher in LVSD group (p<0.05) and anaemia was significantly higher in PSF group than LVSD group (p<0.05).

As shown in [Table/Fig-2], Inotropes, Digoxin and Statins were prescribed significantly more in patients with LVSD group (p<0.05). Calcium channel blockers were prescribed more in PSF group (p<0.05).

As shown in [Table/Fig-3], there were 218 patients discharged after treatment in hospital for heart failure. Higher number of patients with LVSD group were receiving ACE inhibitors, Beta Blockers, Digoxin, Anti-platelets and statins (p<0.05). Calcium channel blockers and amiodarone were prescribed more in PSF group (p<0.05). The treatment outcome in HF patients were measured with respect to three parameters: length of stay in hospital, in-hospital mortality and readmission within 1 month of discharge.

The median length of stay was slightly higher in patients with PSF as compared to LVSD but there was no statistically significant difference between them [Table/Fig-4]. The median length of stay in hospital was slightly more for HF patients with diabetes/hypertension as compared to patients not having the above co-morbidities but there was no statistical significance as shown in [Table/Fig-5,6] respectively.

In-hospital mortality was lower in patients with PSF (6%) than patients with LVSD (20%) and there was statistically significant difference in mortality (p<0.05) between the two groups as shown in [Table/Fig-4]. After multivariable adjustment, patients with PSF had lesser chance of in-hospital mortality compared to patients with LVSD {adjusted 0.2 (95% CI 0.08 to 0.55; p = 0.001)}. Diabetes and Hypertension were not predictors for causing in-hospital mortality in HF patients as shown in [Table/Fig-5-7].

	% Patients with LVSD (n)	% Patients with PSF (n)	p-value (LVSD vs PSF)
1. Demographics			
Mean age (yrs)	56.8 ± 13.2	56.4 ± 15.5	0.083
Male %	75(96)	63(77)	0.042*
2. Medical history %			
Coronary artery Disease	54(69)	20(24)	<0.05*
Hypertension	33(42)	41(50)	0.181
Diabetes (non-insulin treated)	21(27)	17(21)	0.436
Diabetes(insulin treated)	27(34)	16(20)	0.051
Anaemia	7(9)	19(23)	0.017*
Atrial fibrillation	12(15)	14(17)	0.600
Cerebrovascular accident	1(1)	3(3)	0.360
CABG/PTCA	7(9)	5(6)	0.482

[Table/Fig-1]: Demographics and medical history based on ventricular ejection fraction. CABG/PTCA- Coronary artery bypass graft/ percutaneous coronary angiography (n) – no. of patients *p<0.05

Medications	% Patients with LVSD (n)	% Patients with PSF (n)	p-value (LVSD vs PSF)
Inotropes	30(39)	11(14)	<0.05*
Vasodilators	5(7)	4(5)	0.612
ACE inhibitors	30(38)	22(27)	0.173
Angiotensin receptor blockers	8(10)	13(16)	0.170
Calcium channel blockers	7(9)	20(24)	0.003*
Aldosterone antagonists	50(64)	52(64)	0.697
Beta-blockers	18(23)	11(14)	0.148
Loop diuretic	98(125)	94(115)	0.171
Digoxin	59(71)	40(49)	0.002*
Anti-platelets	55(71)	40(49)	0.015
Amiodarone	5(7)	7(9)	0.538
Nitrates	25(32)	18(22)	0.181
Anticoagulants	25(32)	23(29)	0.821
Statins	54(69)	34(42)	0.002*

[Table/Fig-2]: Medication history in heart failure patients based on ventricular ejection fraction.
(n) – no. of patients *p< 0.05

Medications	% Patients with LVSD (n)	% Patients with PSF (n)	P-value LVSD vs PSF
ACE inhibitors	51(52)	31(36)	0.004*
Angiotensin receptor blockers	14(14)	17(19)	0.547
Calcium channel blockers	7(7)	20(23)	0.005*
Aldosterone antagonists	63(65)	58(67)	0.465
Beta-blockers	30(31)	17(20)	0.027*
Loop diuretics	95(98)	97(112)	0.379
Digoxin	67(69)	40(46)	<0.05*
Anti-platelet drugs	62(64)	44(51)	0.009*
Amiodarone	2(2)	9(10)	0.029*
Nitrates	31(32)	20(24)	0.090
Anticoagulants	17(17)	18(21)	0.733
Statins	59(61)	45(52)	0.039*

[Table/Fig-3]: Medication history in heart failure patients at discharge.
(n) – no. of patients *p< 0.05

The percentage of readmissions within one month was slightly higher in patients with PSF (15%) compared to LVSD (14%) but there was no statistically significant difference between the two groups. Diabetes and hypertension were not predictors for causing readmissions within one month in HF patients as shown in [Table/Fig-5-7].

Outcomes measures	Patients with LVSD	Patients with PSF	p-value (LVSD vs PSF)
Admitted patients			
1. Median length of stay in days (Q1, Q3)	6(4,9.7)	7(4,9)	0.48
2. In- hospital Mortality % (n)	20(25)	6(7)	0.001*
Discharged patients			
1. Readmissions within 1 month % (n)	14(14)	15(17)	0.802

[Table/Fig-4]: Measurement of outcome based on ventricular ejection fraction.
(n) - no. of patients * p<0.05.

Outcomes measures	Patients with Diabetes	Patients without diabetes	p-value (Diabetes vs No diabetes)
Admitted patients	n=91	n= 159	
1. Median length of stay in days (Q1, Q3)	7(4,9)	6(4,9.7)	0.304
2. In- hospital Mortality % (n)	10(9)	15(23)	0.297
Discharged patients	n = 82	n = 136	
1. Readmissions within 1 month %(n)	15(12)	14(19)	0.892

[Table/Fig-5]: Measurement of outcome in heart failure patients with or without diabetes.
(n) – No of patients

Outcomes measures	Patients with Hypertension	Patients without Hypertension	p-value (Hypertension vs No hypertension
Admitted patients	n = 92	n = 158	
1. Median length of stay in days (Q1,Q3)	7(4,9)	6(4,9.7)	0.359
2. In- hospital Mortality %(n)	10(9)	15(23)	0.276
Discharged patients	n = 83	n = 135	
1. Readmissions within 1 month %(n)	13(11)	14(20)	0.749

[Table/Fig-6]: Measurement of outcome in heart failure patients with or without Hypertension.
(n) – no. of patients.

	Reference Group	Adjusted* OR (95% CI)	p-value
A) In- hospital mortality			
1. Patients with PSF	Patients with LVSD	0.2 (0.08- 0.55)	0.001**
2. Diabetes mellitus	No diabetes mellitus	0.5 (0.19- 1.37)	0.18
3. Hypertension	No hypertension	1.0 (0.38- 2.77)	0.95
B) Readmissions within one month			
1. Patients with PSF	Patients with LVSD	1.0 (0.41- 2.47)	0.98
2. Diabetes mellitus	No diabetes mellitus	1.3 (0.56- 3.38)	0.47
3. Hypertension	No hypertension	0.7 (0.28- 1.92)	0.54

[Table/Fig-7]: In hospital mortality outcome and readmissions in heart failure patients.
*adjusted for age, gender, coronary artery disease, anaemia, atrial fibrillation, cerebrovascular accident & CABG/PTCA.
**p< 0.05.

DISCUSSION

HF has been one of the most difficult diseases to treat in modern day life. It is important for the treating physician to treat HF at the earliest after detection and also keep a track of the progress of the patient. As there is no cure for this condition, treatment is focused on improving the quality of life of patients by reducing hospital readmissions and preventing mortality of patients.

The present study assessed various parameters like demographics, medical history of HF patients, medications received on admission & discharge and outcome measures. The present study showed more patients in LVSD than PSF group. However, a study by

Fonarow et al., stated that more patients belonged in PSF group than LVSD [10].

The mean age of patients with LVSD were 56.8 ± 13.2 years and patients with PSF 56.4 ± 15.5 years. Although in our study mean age was similar, Fonarow et al., showed that mean age of PSF patients was higher than LVSD patients [10].

Present study showed that males have higher disease preponderance for both LVSD and PSF but study by Fonarow et al., showed higher percentage of male preponderance in LVSD patients [10].

The present study showed higher percentage of LVSD patients were receiving inotropes and nitroglycerine at admission compared to patients with PSF and was consistent with a previous study [11]. Higher numbers of LVSD patients were receiving drugs like ACE inhibitors, beta blockers, digoxin, antiplatelets, nitrates and statins at admission and discharge in comparison to PSF patients. More patients of PSF were receiving calcium channel blockers and angiotensin receptor blockers on admission and discharge compared to LVSD patients. Loop diuretics were prescribed more for LVSD patients than PSF at admission but at discharge they were equally prescribed. The above pattern of medications received at admission and discharge matched with the study conducted by Fonarow et al., [10].

Length of stay in hospital is an important outcome which was measured in our study population. In our study population, the patients with PSF had slightly higher length of stay in hospital compared to LVSD. A report from the OPTIMIZE-HF study reported that median length of stay between the two groups were similar [10]. HF patients with diabetes had a modest increase in length of stay in comparison to patients without diabetes and are consistent with study conducted by Greenberg et al., [12]. The median length of stay in hospital is modestly more in HF patients with hypertension than without hypertension. There are no previous studies showing any comparison of length of stay in hospital among heart failure patients with or without hypertension. However, Ogah et al., showed that median length of stay in HF patients with hypertension was 9 days in his study whereas in our study it is 7 days [13]. Peacock et al., also showed in his study that length of stay in hospital is more than one week in hypertensive HF patients [14].

In hospital mortality of LVSD patients was more than PSF patients in our study. This result was consistent with the study conducted by Fonarow et al., where higher percentage of LVSD patients showed In-hospital mortality [10]. Greenberg et al., showed that in-hospital mortality among HF patients with diabetes and without diabetes were similar [12]. This is not consistent with present study where less mortality was seen in HF patients with diabetes than without diabetes. Present study showed that in-hospital mortality was lower among HF patients with hypertension than without hypertension and is consistent with study conducted by Sato et al., [15]. In our study population we evaluated the number of readmissions occurring within one month post discharge. Kaul et al., showed that HF patients in United States of America and Canada had 20% and 15% chance of readmissions within one month respectively [16]. In the Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan (EVEREST) trial 24% of heart failure patients randomized in the United States were readmitted within 30 days of discharge despite the fact that the majority were treated with evidence-based treatment [17]. In our study higher percentage patients with PSF (15%) had readmission compared to LVSD patients (14%). HF patients with diabetes had a slightly higher percentage of readmissions than without diabetes. However, patients with hypertension had lesser percentage of readmissions than without hypertension. There are no previous studies available for comparison of various groups among HF patients for re admissions of patients within 30 days. Fonarow

et al., showed that percentage of readmissions during 60- 90 day follow-up were similar between LVSD and PSF patients [10]. Greenberg et al., showed higher percentage of readmissions during 60-90 day follow-up in HF patients with diabetes than patients without diabetes [12].

LIMITATION

The limitation of this study is shorter duration of the study. The outcome measures were evaluated only till one month of follow-up. Heart failure is a chronic condition and outcome measures like readmissions and in- hospital mortality are more common at a later time period. Hence the patients have to be evaluated for a longer period to know the actual outcome.

CONCLUSION

Heart failure is one of the most common heart disorders among Indian population. Treatment of heart failure at the right time is most important. Long term monitoring and treatment adherence should be carried out during the course of treatment.

ACKNOWLEDGMENTS

REFERENCES

[1] Mann LD, Chakinala M. Heart failure and Corpulmonale In: Longo DL, Kasper DL, Jameson JL, Fauci AS, Hauser SL, Loscalzo J, editors. Harrison's principles of internal medicine. 18thed. New York: McGraw-Hill Medical Publishing Division; 2011. pp.1901-1910.

[2] Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in Patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation*. 2012;126(1):65-75.

[3] Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8(1):30-41.

[4] Huffman MD, Dorairaj P. Heart failure: Epidemiology and prevention in India. *Natl Med J India*. 2010;23(5):283–88.

[5] Reddy S, Bahl A, Talwar KK. Congestive heart failure in Indians: How do we improve diagnosis and management? *Indian J Med Res*. 2010;132:549-60.

[6] Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for Heart failure : A population based study. *Am J Med*. 2009;122(11):1023-28.

[7] Banumathy S, Rao VD, Joshi L, Govindarajan U. Etiology of congestive heart failure in Indian population – An acute care study of 500 cases. *Journal of Indian college of cardiology*. 2013;3(2):43-48.

[8] Saczynski JS, Go AS , Magid DJ, Smith DH, McManus D, Allen L, et al. Patterns of co-morbidity in older adults with heart failure: the Cardiovascular Research Network PRESERVE study. *J Am Geriatr Soc*. 2013;61(1):26-33.

[9] Cowie MR, Fox KF, Wood DA, Metcalfe C, Thompson SG, Coats AJ, et al.Hospitilization of patients with heart failure: A population base study. *Eur Heart J*. 2002;23(11):877-85.

[10] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50(8):768-77.

[11] Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol*. 2006;47(1):76-84.

[12] Greenberg BH, Abraham WT, Albert NM, Chiswell K, Clare R, Stough WG, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J*. 2007;154(2):277.e1-8.

[13] Ogah OS, Sliwa K, Akinyemi JO, Falase AO, Stewart S. Hypertensive heart failure in nigerian africans: insights from the abeokuta heart failure registry. *J Clin Hypertens* (Greenwich). 2015;17(4):263-72.

[14] Peacock F, Amin A, Granger CB, Pollack CV, Levy P, Nowak R, et al. Hypertensive heart failure: patient characteristics, treatment, and outcomes. *Am J Emerg Med*. 2011;29(8):855-62.

[15] Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, et al. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). *Circ J*. 2013;77(4):944-51.

[16] Kaul P, Reed SD, Hernandez AF, Howlett JG, Ezekowitz JA, Li Y, et al. Differences in treatment, outcomes, and quality of life among patients with heart failure in Canada and the United States. *JACC Heart Fail*. 2013;1(6):523-30.

[17] Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC, et al. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure: results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol*. 2008;52(20):1640-48.

PARTICULARS OF CONTRIBUTORS:
1. Tutor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
2. Associate Professor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.
3. Professor and Head, Department of Cardiology, Kasturba Medical College and Hospital, Manipal University, Manipal, Karnataka, India.
4. Associate Professor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Meena Kumari Kamal Kishore,
Associate Professor, Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, India.
E-mail: mini41178@yahoo.co.in

FINANCIAL OR OTHER COMPETING INTERESTS: None.