

## HIGHER MORTALITY OF DIABETIC PATIENTS IN HEART FAILURE: ROLE OF DIGOXIN

<sup>1</sup>. Kulkarni Avdhoot, <sup>2</sup>. Pandit V.A, <sup>3</sup>. Magdum Ashish,  
<sup>4</sup>. Patil Ravikant, <sup>5</sup>. Udgaonkar Abhijit

1. Assistant professor, Dept of Pharmacology, Bharati Vidyapeeth Deemed University Medical College & Hospital, Sangli, Maharashtra, India.
2. Professor &HOD, Dept.Of Pharmacology, Bharati Vidyapeeth Deemed University Medical College , Pune, Maharashtra.
3. Magdum Ashish, Interventional Cardiologist, Kranti Cardiac Centre, Sangli , Maharashtra.
4. Patil Ravikant, Professor, Dept Of Cardiology, Bharati Vidyapeeth Deemed University Medical College & Hospital ,Sangli, Maharashtra.
5. Udgaonkar Abhijit, Head, Dept. of Transfusion Medicine and Blood Bank, Shri Siddhivinayak Ganapati Cancer Hospital, Miraj, Sangli , Maharashtra

Corresponding Address:

Kulkarni Avdhoot, Assistant professor, Dept of Pharmacology, Bharati Vidyapeeth Deemed University Medical College & Hospital, Sangli, Maharashtra, India.  
Email :apk1982@hotmail.com

### ABSTRACT

**Background:** Digitalis glycosides have been in clinical use in the treatment of congestive heart failure for more than 200 years. Heart failure has a great physical, social and economic impact on patient's life. Diabetes adds to adverse effects of heart failure.

**Aim &objective:** Study was aimed to assess the role of digoxin in patients with heart failure with and without type 2 diabetes and to, access the role of digoxin to reverses NYHA class of patients and number of hospitalization in a year . The outcome of patients of heart failure with and without type 2 Diabetes mellitus was also observed.

**Methodology:** This prospective study has undertaken 70 patients visiting to department of medicine/cardiology at a tertiary health care centre. Patients with heart failure were studied for one year. Data collected with pre-tested questionnaire. Clinical history (specially h/o diabetes mellitus), clinical examination were examined. Patients are treated with drugs like digoxin, beta blockers, ACE inhibitors etc depending upon etiology and symptoms of the patients. Which is followed for upto 1 year and finally the outcomes was measured in terms of reversal of NYHA class, and mortality.

**Results & discussion:** Mean age of the patients was 62.31±3.1 years. Out of 70 patients 36 were male and 34 were female. Diabetic patients were having significantly higher mortality than non-diabetic patients with heart failure. (p<0.05). Digoxin therapy reverses the NYHA class but it is statistically not significant. (p<0.05). In diabetic patients receiving digoxin number of hospitalizations (9/12) were more than that of non-diabetic patients (8/26).

**Conclusion:** Diabetic patients have more adverse effects in heart failure than in non-diabetic patients.

**KEYWORDS :** Cardiovascular diseases, Heart failure, Digitalis, Digoxin, Diabetes.

## **INTRODUCTION**

Cardiovascular diseases (CVDs) generally affect the heart and the circulatory system which include hypertension, Ischemic heart disease (IHD), congestive heart failure (CHF), stroke, peripheral artery disease. Cardiovascular diseases are the major health concern in India and a common cause of early mortality. In the world today 30% of deaths observed due to CVDs including nearly 40% in high-income countries and about 28% in middle and low-income countries.<sup>1</sup> Co morbidities like diabetes have more adverse effects on cardiovascular diseases. Various studies observed that diabetes has more adverse outcome in cardiac patients than non-diabetic patients.<sup>2-6</sup>

Heart failure is a serious condition in which heart is unable to pump enough blood to meet the needs of body. Various drugs are used in treatment of heart failure like diuretics, angiotensin-converting enzyme inhibitors, beta-blockers and digitalis glycosides. Digitalis is extracted from the leaves of the foxglove plant. It stimulates heart muscle. The drug has been used for over two centuries to treat heart failure. In patients with heart failure, the positive inotropic effects of the digitalis glycosides are beneficial. Digitalis glycosides are the only group of positive inotropic drugs that persistently increase the ejection fraction during long-term administration in patients with heart failure thus Digoxin is used to decrease the symptoms and increase the exercise capacity in patients with congestive heart failure. Digoxin is widely used in treatment of heart failure.

Various studies were done to see the effects of digoxin in heart failure patients. Very few studies were done to see the effects of digoxin in heart failure patients with diabetes so this study was conducted to see the role of digoxin in heart failure patients with diabetes. So the present study was thus designed to assess the role of digoxin in patients with heart failure with and without type 2 diabetes and does digoxin reverses NYHA class of patients and number of hospitalization in a year and to observe the outcome of patient of heart failure with and without type 2 Diabetes mellitus

## **MATERIALS AND METHODS**

Present study was a Prospective, observational multicentric, open label study, carried out on patients at tertiary care hospitals, who are undergoing for treatment of heart failure.

Study was approved by institutional ethical committee of the institute. A valid written consent was taken from patients after explaining study to them.

### **Study design**

**Inclusion criteria:** 1. Age more than 18 years 2. Either sex 3. Patients presented to hospital with diagnosis of CHF 4. Patients of NYHA class 2 and 3

**Exclusion criteria:** 1. Patients not willing to participate 2. Patients with acute coronary syndrome 3. Patients with Chronic obstructive pulmonary disease 4. Patients with history of asthma 5. End-stage renal failure 6. Previous history of hepatic cirrhosis 7. Isolated right HF

Total 70 patients studied after considering inclusion and exclusion criteria.

### **Data collection:**

Data was collected with pre-tested questionnaire. Data included sociodemographic data, clinical history of the patient. Past clinical symptoms (limitation of activity, fatigue, and dyspnoea or orthopnoea), signs (edema, elevated jugular venous pressure, rales, or a gallop rhythm) were recorded. A thorough clinical examination was done. History of diabetes, NYHA classification of patient, etiology of cardiac failure was noted.

Patient underwent necessary investigations. Patients were treated with ACE Inhibitors, B blockers, Digoxin etc. in this study we are concentrated on effect of digoxin. Digoxin was given randomly to the patients. Patient was followed for every 4 weeks and 16 weeks and then after every 4 months .last follow up was done after one year. Outcome was measured in terms of mortality, no of hospitalizations and change in NYHA classification. Data was analysed with appropriate statistical tests.

### **RESULTS**

Total 70 patients were studied. Majority of the patients were in the age group of 61-70 years (40%) followed by 51-60 years (24.28%). In non-diabetic patients majority of the patients were from age group of 61-70 years and 51-60 years. In case of diabetic patients majority patients were from age group of 61-70 years and 71-80 years. Mean age of the patients was  $62.31 \pm 3.1$  years as shown in table 1 (distribution of patients according to age group and diabetic status of the patients.) Out of 70 patients 36 were male and 34 were female. Similar distribution was observed in non-diabetic patients and diabetic patients as

shown in table 2 (Distribution of patients according to variables and diabetic status of patient). Among all 70 patients 4 (5.71%) patients were defaulters and 66 (94.29%) were having regular follow up without any default. In case of diabetic patients none of the patient was defaulter. In non-diabetic patients 4 patients were defaulters.

In case of etiology majority of the patients were having non-ischaemic etiology (57.14%) and 42.86% were having ischaemic etiology. In diabetic patients ischaemic etiology was observed in 67.86% and 32.14% were having non-ischaemic etiology. In case of non-diabetic patients 73.81 % were having non-ischaemic etiology and 26.19% were having ischaemic etiology. Among non-diabetic patients 88.1% patients were alive after 1 year and 11.9% were dead. In diabetic patients 71.42% were alive and 28.58% were dead.

Thus diabetic patients were having significantly higher mortality than non-diabetic patients with heart failure. ( $p < 0.05$ ). Table 3 shows distribution of patients according to outcome and diabetic status. At the start of study among non-diabetic patients, majority patients (80.95%) were from NYHA II class followed by 19.05% were from NYHA III class. In diabetic patients 57.14% were from NYHA II class and 42.86% were from NYHA III class. At the start of study there were 18 patients in class II and 14 patients in class III among patients receiving digoxin. At the end of one year follow up 11 patients were reversed to class I. There were 9 patients in class II and only 1 patient in class III. 8 patients were dead and 1 was defaulter as shown in table 5 (Comparison of patients according to NYHA class at start of study and after one year follow up and digoxin therapy in patients).

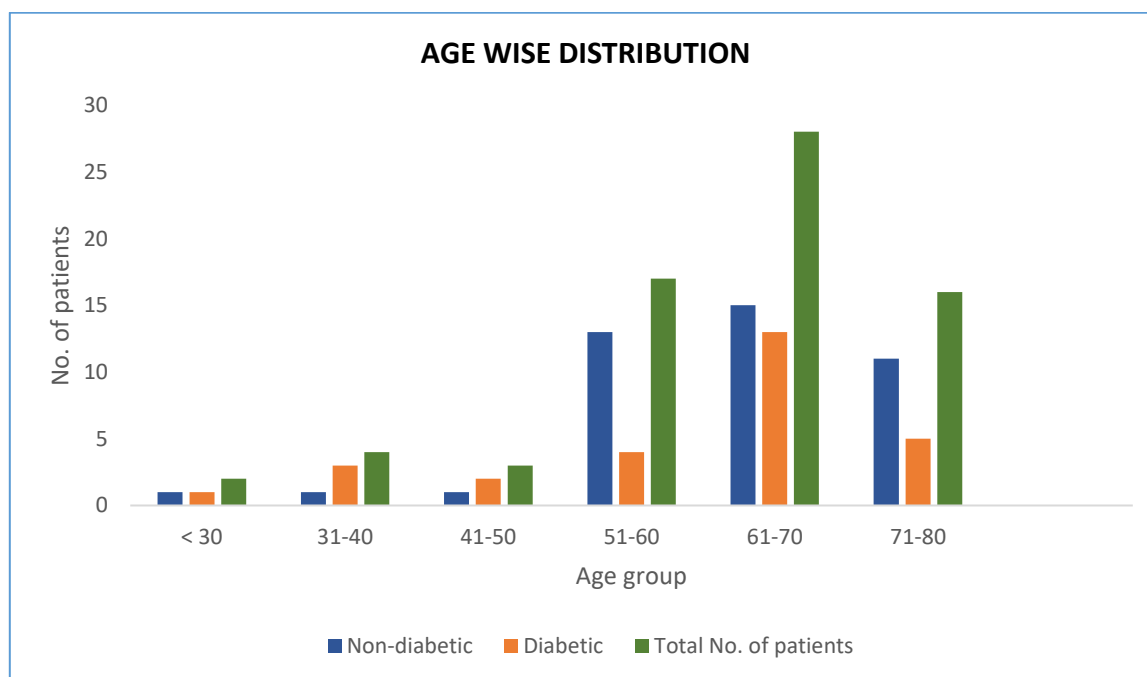
In case of patients without digoxin therapy there were 32 patients in class II and 6 patients in class III. At the end of one year 25 patients were reversed to class I. 6 patients were in class II and one in class III. Among these patients 5 patients were dead and 1 was defaulter. Thus we can see that digoxin therapy reverses the NYHA class but it is statistically not significant. ( $p < 0.05$ )

We can observe that no of hospitalizations were more in patients receiving digoxin. No of hospitalizations were more in diabetic patients with digoxin therapy (19/16) and less in non-diabetic patients (10/16). Here in some cases numerator is more than denominator because one patient is hospitalized for more than one time may be 2 or 3 times as shown in table 6 (Comparison of patients according to no of hospitalizations with or without digoxin and diabetic status of the patient). In diabetic patients receiving digoxin no of hospitalizations

(9/12) were more than that of non-diabetic patients (8/26). This difference is statistically significant. ( $p < 0.05$ )

**Table 1: Distribution of patients according to age group and diabetic status**

	Age group (years)	Non-diabetic	Diabetic	Total No. of patients
1	< 30	01	01	02 (2.86%)
2	31-40	01	03	04(5.71%)
3	41-50	01	02	03(4.29%)
4	51-60	13	04	17(24.28%)
5	61-70	15	13	28(40%)
6	71-80	11	05	16(22.86%)
7	Total	42	28	70(100%)



**Fig. 1: Distribution of patients according to age group and diabetic status**

**Table 2: Distribution of patients according to variables and diabetic status**

Sr no	Variables	Non-diabetic	Diabetic	Total
1	<b>Gender</b>			
2	Male	22(52.38%)	14(50%)	36(51.43%)
3	Female	20(47.62%)	14(50%)	34(48.57%)
4	<b>Defaulter status</b>			

5	Defaulter	04 (9.52%)	00 (0%)	04(5.71%)
6	Non-defaulter	38(90.48%)	28(100)	66(94.29%)
7	<b>Etiology</b>			
8	Ischaemic	11(26.19%)	19(67.86%)	30(42.86%)
9	Non-ischaemic	31(73.81%)	09(32.14%)	40(57.14%)

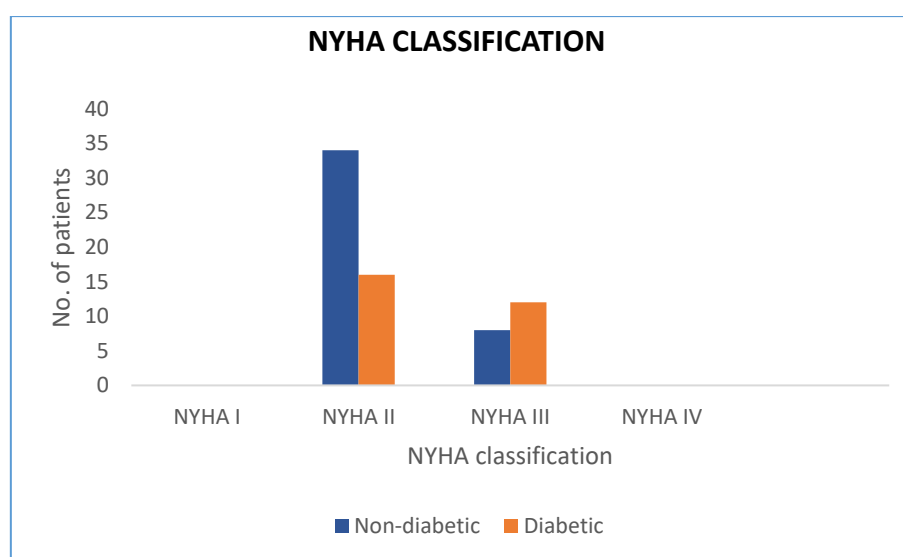
**Table 3: Distribution of patients according to outcome and diabetic status**

Outcome	Non-diabetic	Diabetic
Alive	37(88.1%)	20(71.42%)
Dead	05(11.9%)	08(28.58%)
Total	42 (100%)	28 (100%)

P <0.05 statistically significant

**Table 4: Distribution of patients according to NYHA classification and diabetic status**

	Non-diabetic	Diabetic
NYHA I	00 (0%)	00 (0%)
NYHA II	34 (80.95%)	16 (57.14%)
NYHA III	08 (19.05%)	12 (42.86%)
NYHA IV	00(0%)	00(0%)
Total	42 (100%)	28 (100%)



**Fig 2: Distribution of patients according to NYHA classification and diabetic status**

**Table 5: Comparison of patients according to NYHA class at start of study and after one year follow up and digoxin therapy in patients**

NYHA classification	With Digoxin		Without digoxin	
	No of patients at start of study	No of patients after one year	No of patients at start of study	No of patients after one year
NYHA I	00	11	00	25
NYHA II	18	09	32	06
NYHA III	14	01	06	01
NYHA IV	00	00	00	00
Total	32	21*	38	32**

\*Dead (8), defaulter (3) \*\* Dead (5), defaulter (1)

**Table 6: Comparison of patients according to no of hospitalizations with or without digoxin and diabetic status of the patient**

Diabetic status of patient	No of hospitalization With Digoxin therapy	No of hospitalization Without digoxin therapy	Total
Diabetic	19/ 16	09/12	28
Non-diabetic	10/16	08/26	18
Total	29/32	17/38	46

## DISCUSSION

Majority of the patients were in the age group of 61-70 years (40%) followed by 51-60 years (24.28%). In case of diabetic patients majority patients were from age group of 61-70 years and 71-80 years. Mean age of the patients was  $62.31 \pm 3.1$  years. Various studies have mean age of the patient ranging from 69-77 years.<sup>7-10</sup> this difference in age group may be earlier manifestation of disease in our country, less effective treatment and the study population composition. Ethnicity changes the manifestations and outcome in the study group. Dries et al.,<sup>11</sup> compared HF evolution between Caucasians and blacks, and found higher mortality among blacks; Rathore et al.<sup>12</sup> showed lower mortality among blacks hospitalized for HF; in contrast to above Mathew et al.<sup>13</sup> showed no difference in mortality between the ethnicities.

Among non-diabetic patients 88.1% patients were alive after 1 year and 11.9% were dead. In diabetic patients 71.42% were alive and 28.58% were dead. Thus diabetic patients were having significantly higher mortality than non-diabetic patients with heart failure. ( $p < 0.05$ ). Similar to our findings various studies showed that diabetic patients have higher mortality than non-diabetic patients in heart failure.<sup>2-6</sup> In case of patients without digoxin therapy there were 32 patients in class II and 6 patients in class III. At the end of one year 25 patients were reversed to class I. 6 patients were in class II and one in class III. Among these patients 5 patients were dead and 1 was defaulter. Thus we can see that digoxin therapy reverses the NYHA class but it is statistically not significant ( $p < 0.05$ ).

No of hospitalizations were more in diabetic patients with digoxin therapy (19/16) and less in non-diabetic patients (10/16). In diabetic patients receiving digoxin no of hospitalizations (9/12) were more than that of non-diabetic patients (8/26). Similar study was done by DIG trial<sup>14</sup> where they studied 6800 patients, those with diabetes ( $n = 1933$ ) were older, more often women, had worse clinical status and more co-morbidity than those without diabetes. All-cause and CV mortality were higher in patients with diabetes than in those without and digoxin. The rate of HF hospitalisation (per 100 person-years) in patients with diabetes was higher than in those without and was reduced by digoxin in both patient groups. The difference in our findings may be due to the fact that DIG trial patients were not receiving betablockers and thus those findings may not be applied to our study where we used beta blockers. Also our study didn't reveal detailed cause of death in all patients. Digoxin is recommended in symptomatic heart failure patients with reduced ejection fraction (HF-REF) in sinus rhythm so there may be increased no of hospitalization in patients with reduced ejection fraction.

## **CONCLUSION**

CVDs can be congenital or acquired throughout people's lifespan. Atherosclerosis, rheumatic heart disease, and cardiovascular inflammation are the main and more prevalent cardiovascular acquired problems. Cardiovascular diseases are multifactorial and several modifiable and non-modifiable risk factors and unhealthy lifestyles are involved; however, these risks and behaviours cannot completely explain the incidence of cardiovascular events. Diabetes is a prime risk factor of cardiovascular diseases so in the present study an effort was made to assess the role of digoxin in patients with heart failure with and without type 2



diabetes and from the research findings it can be concluded that diabetic patients have more adverse effects in heart failure than in non-diabetic patients.

## REFERENCES

1. Gaziano TA, Gaziano JM. Epidemiology of Cardiovascular Disease. In: Lango DL (ed.). Harrison's Principles of Internal Medicine. 18th edn. New York: McGraw Hill 2012;2012:1811-6.
2. Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, Tschoepe D, Doehner W, Greene SJ, Senni M, Gheorghiade M, Fonarow GC. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail.* 2015;3:136-45.
3. Dei Cas A, Fonarow GC, Gheorghiade M, Butler J. Concomitant diabetes mellitus and heart failure. *Curr Probl Cardiol.* 2015; 40: 7-43.
4. MacDonald MR, Petrie MC, Hawkins NM, Petrie JR, Fisher M, McKelvie R, Aguilar D, Krum H, McMurray JJ. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J.* 2008;29:1224-40.
5. Suskin N, McKelvie RS, Burns RJ, Latini R, Pericak D, Probstfield J, Rouleau JL, Sigouin C, Solymoss CB, Tsuyuki R, White M, Yusuf S. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure. *Eur Heart J.* 2000;21:1368-75.
6. MacDonald MR, Petrie MC, Varyani F, Ostergren J, Michelson EL, Young JB, Solomon SD, Granger CB, Swedberg K, Yusuf S, Pfeffer MA, McMurray JJ; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J.* 2008;29:1377-85.
7. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardes-Pereira S, Berwanger O, et al; Investigadores Estudo BREATHE. I Brazilian Registry of Heart Failure - Clinical Aspects, Care Quality and Hospitalization Outcomes. *Arq Bras Cardiol.* 2015;104(6):433-42.
8. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ.* 2012;184(14):E765-73.

9. Fonarow GC; ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med.* 2003;4(7):S21-30.
10. Gyalai-Korpos I, Ancusa O, Dragomir T, Tomescu MC, Marincu I. Factors associated with prolonged hospitalization, readmission, and death in elderly heart failure patients in western Romania. *Clin Interv Aging.* 2015;10:561-8.
11. Dries DL, Strong MH, Cooper RS, Drazner MH. Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. *J Am CollCardiol.* 2002;40(2):311-7
12. Rathore SS, Foody JM, Wang Y, Smith GL, Herrin J, Masoudi FA, et al. Race, quality of care, and outcomes of elderly patients hospitalized with heart failure. *JAMA.* 2003;289(19):2517-24.
13. Mathew J, Wittes J, McSherry F, Williford W, Garg R, Probstfield J, et al; Digitalis Investigation Group. Racial differences in outcome and treatment effect in congestive heart failure. *Am Heart J.* 2005;150(5):968-76.
14. Abdul-Rahim, A. H., MacIsaac, R. L., Jhund, P. S., Petrie, M. C., Lees, K. R., and McMurray, J. J.V. (2016) Efficacy and safety of digoxin in patients with heart failure and reduced ejection fraction according to diabetes status: An analysis of the Digitalis Investigation Group (DIG) trial. *International Journal of Cardiology*, 209, pp. 310-316.