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A study of worsening renal function during therapy of cardiovascular disease and assessment of its prognosis

Thomas Zacharia[1], Anju Joseph[2], Anu J[3], Anu Philip[4], Aswathy Jai Kumar*[5]

[1]*Faculty, Department of Pharmacy Practice, Sri Ramakrishna Institute of Paramedical Sciences (SRIPMS), Coimbatore, Tamil Nadu-641044*
[2]*Pharm.D Intern, SRIPMS, Coimbatore, Tamil Nadu-641044*
[3]*Pharm.D Intern, SRIPMS, Coimbatore, Tamil Nadu-641044*
[4]*Pharm.D Intern, SRIPMS, Coimbatore, Tamil Nadu-641044*
[5]*Pharm.D Intern, SRIPMS, Coimbatore, Tamil Nadu- 641044*

***Corresponding Author: Aswathy Jai Kumar**
Email id: aswathy.ajk33@gmail.com

ABSTRACT

Background and Aims

Cardiovascular disease is a class of diseases that involves the heart, the blood vessels or both. In patients with cardiovascular diseases, with reduced renal perfusion, it is common to encounter worsening of renal function during the hospital stay. This study was carried out to identify worsening renal function in patients with cardiovascular disease from their renal parameters and to assess the prognosis of the disease in the study population.

Methods and Results

This observational study conducted over a 6 month period found that at presentation, the major diagnosis was Hypertension (96.77%) with the majority of the drugs given to the patients being Anti Hypertensive (16%). Eighteen patients (29.5%) showed Worsening Renal Function. To these patients, Aspirin and Clopidogrel, two nephrotoxic drugs were prescribed during both therapy and discharge. Interactions such as Atorvastatin vs Pantoprazole (25.80%) and Ceftriaxone vs Furosemide (16.12%), both of which can worsen the renal function were identified.

Conclusion

It can be concluded that worsening renal function occurs frequently among hospitalized cardiovascular patients and that clinical characteristics available at hospital admission can be used to identify both the predictors and the patients at increased risk for worsening renal function.

Keywords: Cardiovascular disease, Worsening renal function, Nephrotoxicity, Prognosis

INTRODUCTION

Cardiovascular disease generally refers to conditions that involve narrowed or blocked blood vessels that can lead to a heart attack, chest pain (angina) or stroke. Other heart conditions, such as those that affect your heart's muscle, valves or rhythm, also are considered forms of heart disease [4].Every year, an estimated 17 million people globally die of cardiovascular diseases (CVD), particularly heart attacks and strokes [6]. In India,

heart ailments have replaced communicable diseases as the biggest killer. According to recent data, approximately 30 percent of the urban population and 15 percent of the population living in rural areas suffer from high blood pressure and heart attacks. As the risk factors of heart ailments increase, so does the mortality rate.

Ejection fraction (EF) is the fraction of outbound blood pumped from the heart with each heartbeat. It is commonly measured by echocardiogram and serves as a general measure of a person's cardiac function. The heart and the kidneys are involved in maintaining hemodynamic stability and organ perfusion through an intricate network. These two organs communicate with one another through a variety of pathways in an interdependent relationship. A characteristic of the failing heart is a reduction of cardiac output. This reduction in cardiac output leads to reduced net renal perfusion. Thus it is highly essential that certain biomarkers be used to assess the renal function during cardiac therapy especially in pre and post operative surgery as the renal function largely determines the patient's morbidity and mortality during surgeries as well as post-operative recovery.

Some common markers used to estimate renal function are Glomerular filtration rate (GFR), Creatinine Clearance CCr, Estimated GFR (eGFR) etc. Several studies of patients with heart failure (HF) have reported an association between impaired renal function and unfavorable outcomes [1-8]. The change in renal function during hospitalization for cardiovascular diseases may also have prognostic importance. Daniel E et al in a study on the Incidence, Predictors at Admission, and Impact of Worsening Renal Function among Patients Hospitalized with Heart Failure and concluded that the Worsening renal function (WRF) occurs frequently among hospitalized HF patients and is associated with significantly worse outcomes and thus poorer prognosis.

Here we designed a study that aims to assess the renal function and thus sought to assess the prognosis of the disease in these patients with worsening renal function.

MATERIALS AND METHODS

This study was carried out in a 700 bedded multispecialty tertiary care private corporate hospital. This Prospective observational study was conducted among 60 patients for duration of 6 months between December 2014 and May 2015 and was carried out after obtaining the consent of from the hospital authorities and the patients.

Inclusion criteria

CVD patients of either sex admitted in the study site during the study period and willing to participate.

Exclusion criteria

Patients with insufficient data, critically ill, having prior history of renal failure, Pediatric patients (below 18 yrs.) as well as pregnant women, and patients who are not willing to participate are excluded from the study.

The principal outcome was WRF, defined as an increase in serum creatinine of >0.3 mg/dl from admission, consistent with several previous investigations. Patients with worsening renal function were identified based on laboratory data and clinical evaluation. Verbal consent was obtained from each subject before initiating the study. Structured preform were used to collect various clinical and demographic details of the patient such as age, gender, length of hospital stay, primary diagnosis, serum creatinine, urea, uric acid, creatinine clearance and ejection fraction. Treatment data including prescribed drugs, dosages and frequency were also recorded. These data were then assessed.

RESULTS

Patient baseline characteristics are listed in Table 1. Mean age (±SD) of the study population was 55.7±15.9 years. Nearly half the total population was male with a frequency of 49(80.3%), while the remaining 12(19.7%) were female. 59% of the subjects were found to be smokers and 44.3% alcoholics. Demographic details of these patients are shown in Table 2. 32 patients out of 61 were showing normal EF (52.5 %) and EF dysfunction was shown by 29(47.5%) of the subjects (Table 1). At presentation, the major diagnoses were Hypertension (96.77%), Ischemic Heart Disease (83.87%) and Diabetes mellitus (64.51%) [Fig 1] (Table 3)

Majority of the drugs prescribed were Anti Hypertensive drugs (16.02%), Anti coagulants/Anti

platelets (10.61%) and antibiotics (10.23%) [Fig 2] (Table 4). Worsening renal function occurred in 18 patients (29.5%) [Fig 3]. On assessing the nephrotoxic drugs given to the WRF patients undergoing CVD therapy, the major drugs prescribed were Heparin (11.21%), Aspirin (10.28%) and Clopidogrel (9.34%) during therapy [Fig 4], while the major drugs prescribed at discharge were Statins(16.36%), Aspirin (14.54%) and Clopidogrel (12.72%)[Fig 5]. Both **Clopidogrel and Aspirin**, two known nephrotoxic agents were prescribed to the patients both upon discharge and during the hospital stay. On assessing the drug interactions among the patients with WRF, the most common interacting drugs were identified as Atorvastatin vs. Pantoprazole and Ceftriaxone vs furosemide. These interactions were found in 25.80 % and 16.12 % of patients respectively (Fig 6) (Table 5)

Out of the 61 patients studied only 29(48%) showed EF dysfunction, while among the WRF patients 16(89%) showed EF dysfunction (Table 1). Similarly hypertension was shown by 61% of the WRF population. Both are major risk factors for WRF. Two nephrotoxic drugs and two drug interactions causing nephrotoxicity can contribute to worsening renal function here. With the Worsening of renal function, the prognosis of these patients will also be poor. 30% of the total population shows poor and 70% of the population shows good prognosis.

TABLE 1: BASELINE CHARACTERISTICS OF THE CARDIOVASCULAR PATIENTS

			WRF				
	Total(61)		**No(43)**		**Yes(18)**		
	#	**%**	**#**	**%**	**#**	**%**	**p value**
Demographics							
Age: mean (SD)	55.07	15.9					0.989
Male	49	80.3%	35	57.4	14	23.0	0.746
Female	12	19.7%	8	13.1	4	6.6	
Smoker	36	59.0	11	61.6	7	38	0.432
Alcoholic	27	44.3	8	44.4	10	55	0.559
Ejection fraction							
Normal(LVEF ≥50)	32	52.5	2	11.1	16	88.8	**0.000***
EF dysfunction(50 <LVEF)	29	47.5	16	88.8	2	11.1	**0.000***
Medical history							
Prior heart failure	28	45.9	9	50	8	44	0.883
Hypertension	34	55.7	7	38	11	61	0.585
Atrial fibrillation	7	11.5	15	83	3	16.6	0.410
Diabetes Mellitus	29	47.5	10	55.5	8	44	0.754
Stroke	2	3.3	17	94.4	1	5.5	0.518
Myocardial infarction	5	8.2	15	83	3	16.6	0.119
Angina	5	8.2	16	88.8	2	11.1	0.591

TABLE 2: DEMOGRAPHICS DATA

S.No	Parameters	Values
1.	N	61
2.	Mean age	55.7±15.916
3.	Male	49(80.3%)
4.	Female	12(19.7%)
5.	Mean Creatinine	1.55 ± 0.802
6.	Mean weight	69.94±1.06
7.	Mean Urea	42.45± 22.95
9.	Mean Creatinine clearance	62.503±22.22

TABLE 3: CLINICAL CONDITIONS OF PATIENTS

S.No	Clinical conditions	No. of patients	Percentage (%)
1.	Hypertension	30	96.77
2.	Ischemic Heart Disease	26	83.87
3.	Diabetes mellitus	20	64.51
4.	Left ventricular Dysfunction	16	51.61
5.	Renal Impairment	11	35.48
6.	CAD	9	29.03
7.	MI	9	29.03
8.	Chronic obstructive pulmonary disease	8	25.80
9.	Mitral Stenosis	6	19.35
10.	Congestive heart failure	5	16.12
11.	Pulmonary arterial hypertension	5	16.12
12.	Acute Pulmonary Edema	4	12.90
13.	Atrial Fibrillation	4	12.90
14.	CHF	4	12.90
15.	Congestive cardiac failure	4	12.90
16.	Angina pectoris	3	9.67
17.	Dyslipidemia	3	9.67
18.	LRTI	3	9.67
19.	Acute gastroenteritis	2	6.45
20.	Acute myocardial wall infarction	2	6.45
21.	Dilated Cardiomyopathy	2	6.45
22.	Trivial AR	2	6.45
23.	Anemia	1	3.22
24.	Atypical Chest Pain	1	3.22
25.	Diabetic neuropathy	1	3.22
26.	Hypertensive urgency	1	3.22
27.	Hyperurecemia	1	3.22
28.	Hypothyroidism	1	3.22
29.	Stroke	1	3.22
30.	Supraventricular tachycardia	1	3.22
31.	Triple vessel disease	1	3.22

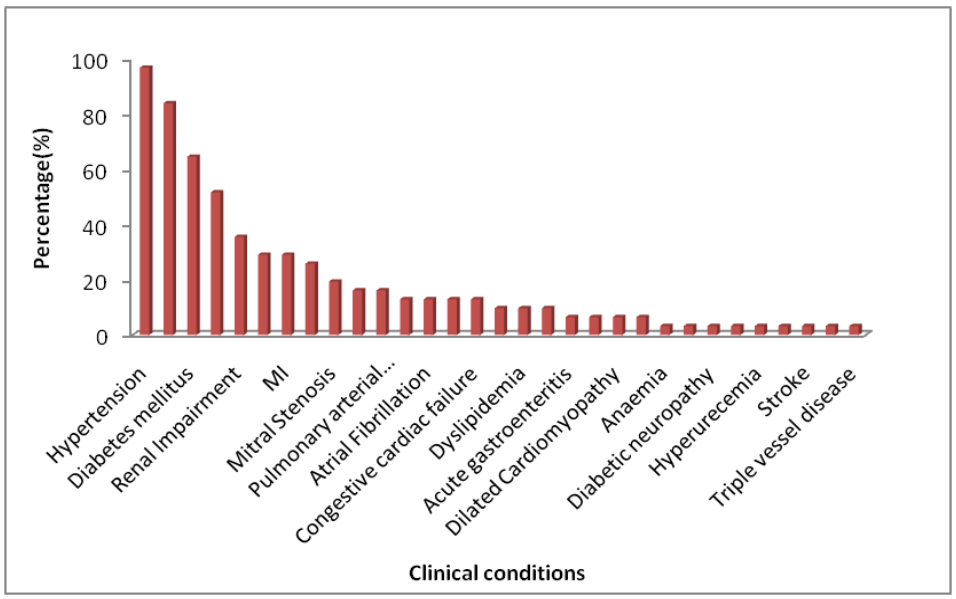

Fig 1: The distribution of the different clinical conditions among the patient population. Values are expressed as percentage.

TABLE 4: PRESCRIBING PATTERNS OF DRUGS IN CARDIOVASCULAR PATIENTS

S. No.	Category	Total drugs	Percentage (%)
1.	Anti hypertensives	83	16.02
2.	Anti coagulants/Anti platelets	55	10.61
3.	Antibiotics	53	10.23
4.	Diuretics	52	10.03
5.	Proton Pump Inhibitors	47	9.07
6.	Vitamins and minerals	35	6.75
7.	Dyslipidaemic agents	32	6.17
8.	Anti diabetics	25	4.82
9.	Anti asthmatic/Bronchodilators	21	4.05
10.	Anti angina	18	3.47
11.	Cardiac glycosides	14	2.70
12.	NSAIDS	13	2.50
13.	Anti anxiety/Anxiolytics	12	2.31
14.	Anti arrhythmic	11	2.12
15.	Anti emetics	9	1.73
16.	Anti gout	8	1.54
17.	Anti convulsants	5	0.96
18.	Miscellaneous	3	0.57
19.	Mucolytics and antitussives	3	0.57
20.	Anti ulcer	2	0.38
21.	Probiotics	2	0.38
22.	Corticosteroids	2	0.38
23.	Renal Protectant	2	0.38
24.	Anti histamine	2	0.38
25.	Anthelmintics	2	0.38
26.	Anti histamines	2	0.38
27.	Thyroid drugs	2	0.38
28.	Anti diarrhoeals	2	0.38
29.	Neurotonics	1	0.19

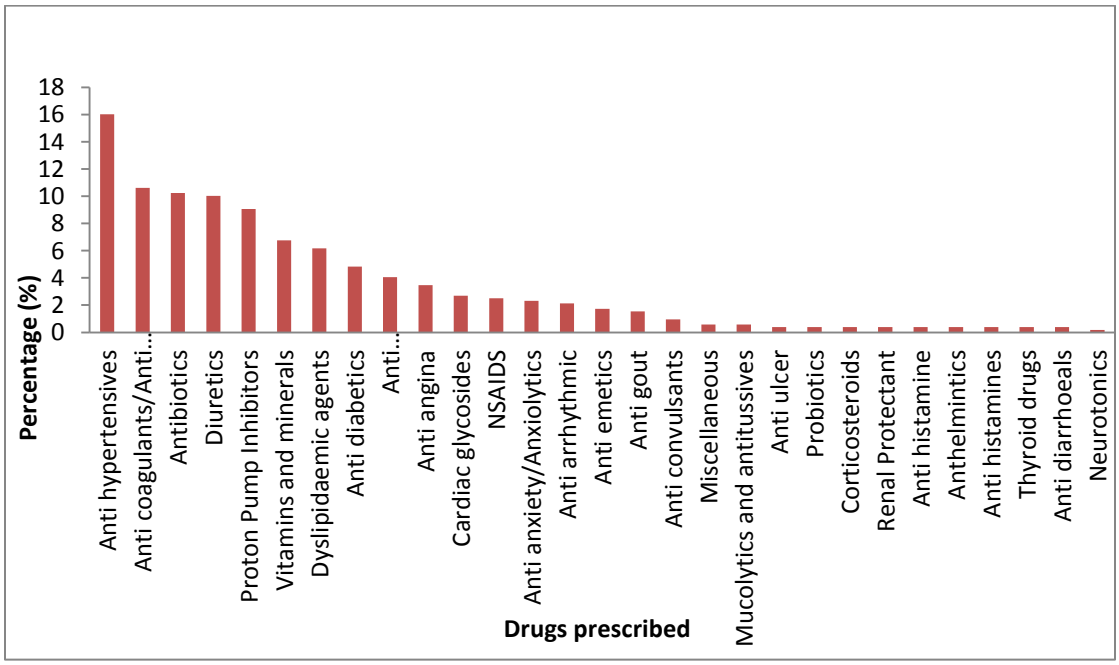

Fig 2: Prescribing patterns of all the drugs used by the CVD patients in this study. Values are expressed in terms of percentage.

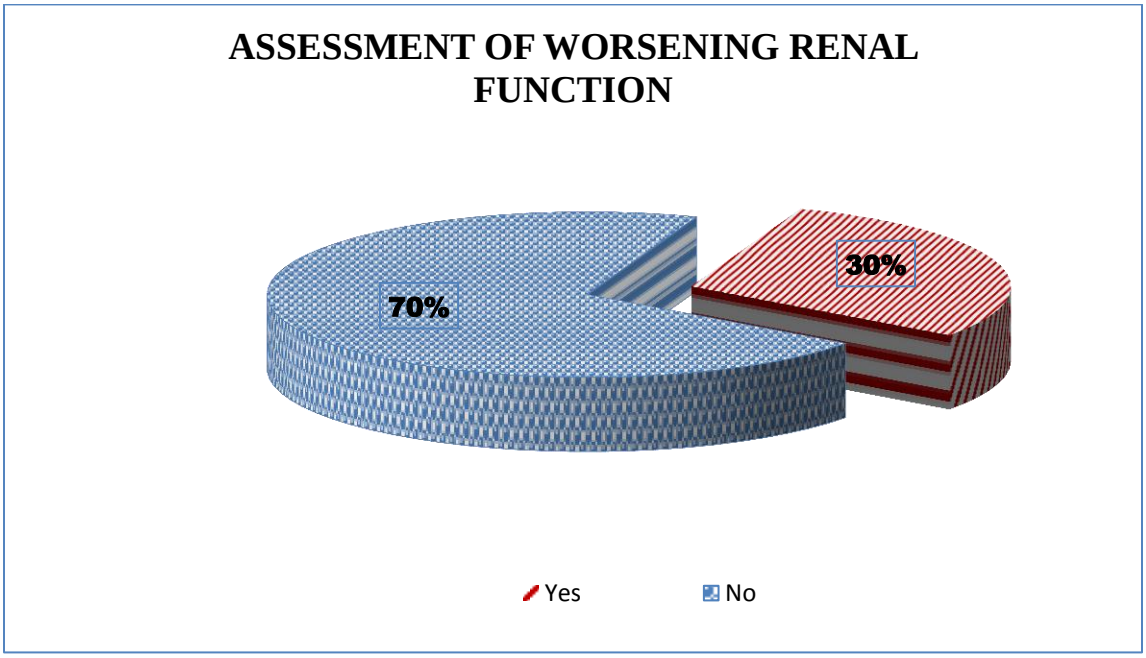

Fig 3: The ratio of worsening renal function in the study population, expressed in terms of percentage.

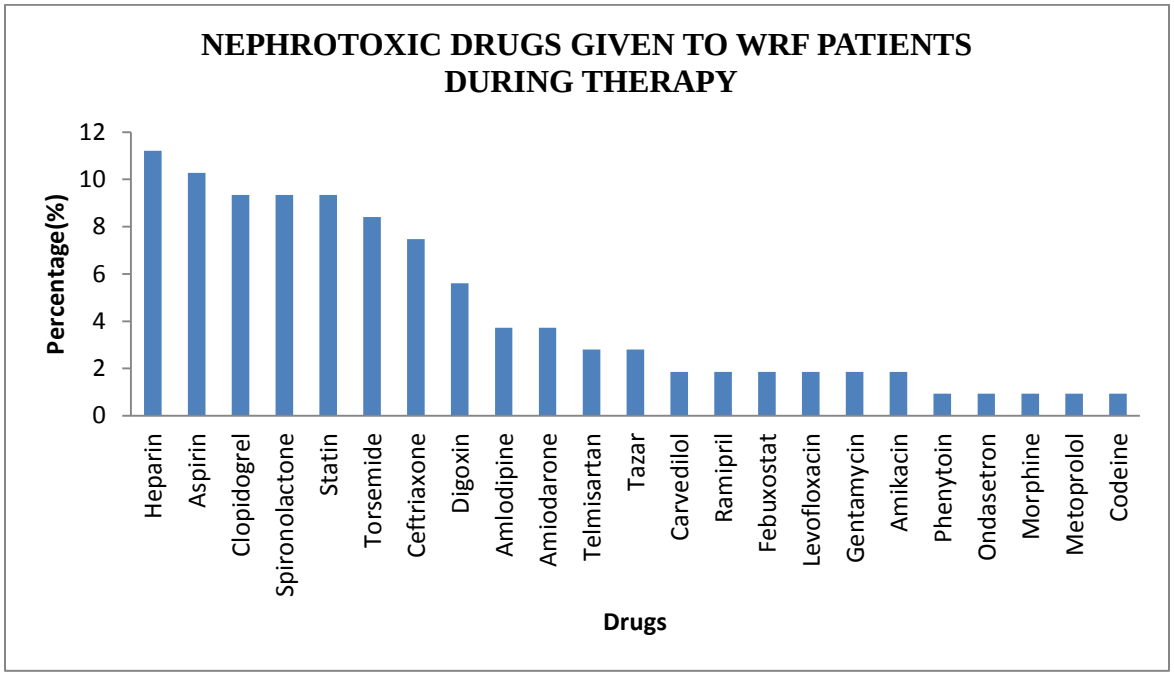

Fig 4: The assessment of nephrotoxic drugs given to WRF patients during cardiovascular therapy, expressed in terms of percentage.

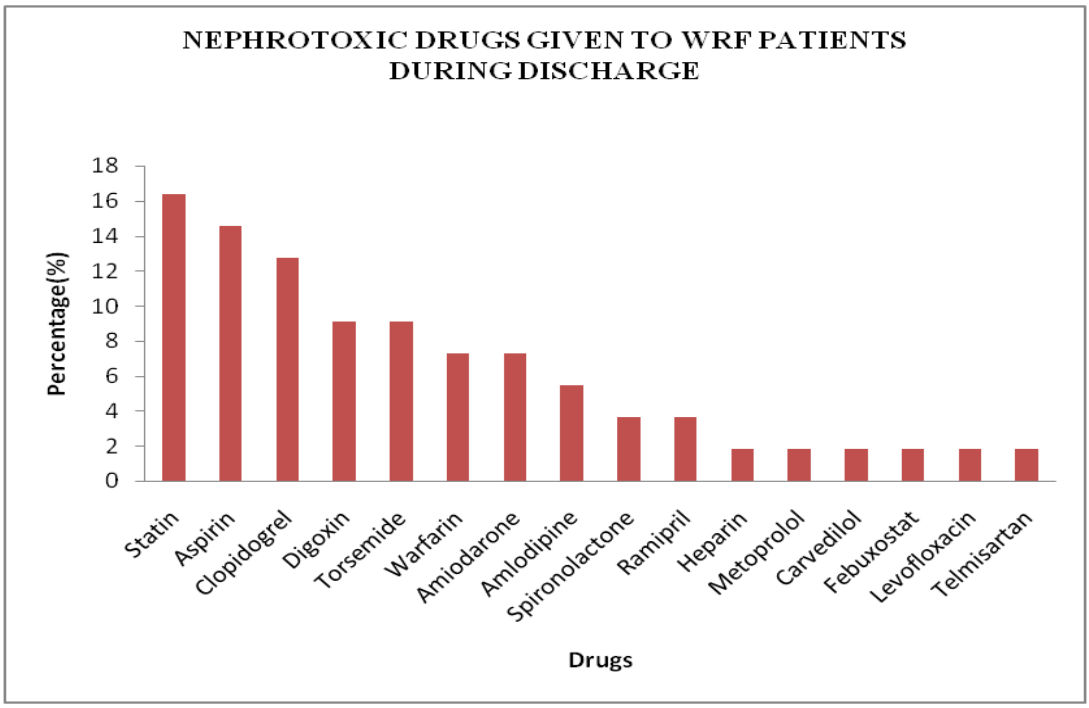

Fig 5: The assessment of nephrotoxic drugs given to WRF patients undergoing CVD therapy, at discharge. Values are expressed in terms of percentage.

TABLE 5: ASSESSMENT OF DRUG INTERACTIONS IN WRF PATIENTS DURING CARDIOVASCULAR THERAPY

Drug interactions	No. of patients	Percentage (%)
Atorvastatin+Pantoprazole	8	25.80
Ceftriaxone+furosemide	5	16.12
Heparin+Spironolactone	3	9.67
Furosemide+Gentamycin	2	6.45
Ceftriaxone+torsemide	2	6.45
Spironolactone+Ramipril	2	6.45
Amiodarone+Atorvastatin	2	6.45
Amiodarone+digoxin	1	3.22
Amikacin+Torsemide	1	3.22
Heparin+Ramipril	1	3.22
Digoxin+torsemide	1	3.22
Aspirin+Telmisartan	1	3.22
Metoprolol+Aspirin	1	3.22
Amikacin+Furosemide	1	3.22

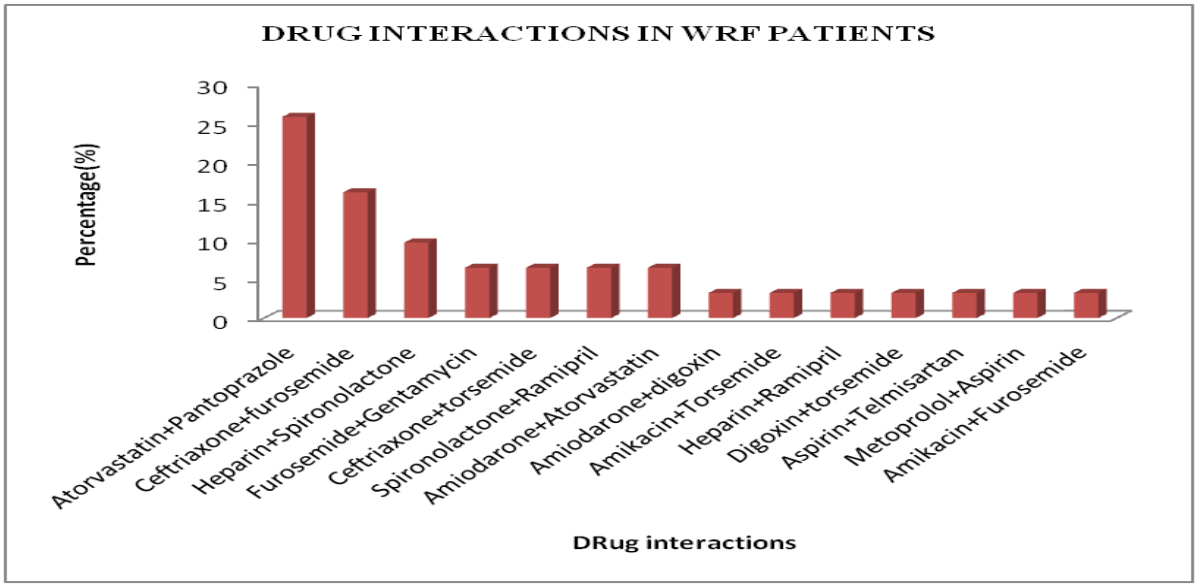

Fig 6: The assessment of drug interactions seen in WRF patients (N=18). Values are expressed in terms of percentage.

DISCUSSION

The present study adds to the growing evidence that WRF is common among patients hospitalized for HF. The principal findings are: 1) 29.5% of patients develop WRF, as defined by serum creatinine increase ≥ 0.3 mg/dl, a previously identified threshold associated with worse outcomes; 2) 30% of the study population shows a poor prognosis. The risk associated with post-admission WRF was first reported in a study limited to older HF patients (mean age 79 ±8 years; 44% age over 80 years) that showed a similarly high incidence of WRF (28%) [9]. Both the previous and the present studies demonstrate that WRF occurs early, appearing here within the first 3 days in 72% of the patients.

The early occurrence of WRF in the course of hospitalizations for CVD patients suggests that renal deterioration is related to inherent mechanisms of disease or to the impact of therapy administered upon admission, rather than to progressively worsening clinical status over prolonged hospitalization. The mechanisms responsible for WRF are complex and not well-defined. Co-morbid conditions or the treatments utilized may also play a critical role in the development of WRF. It was found that nearly half the total population was male most of them in their late adulthood (51-65 yrs) with 59% of the subject's smokers and 44.3% alcoholics. Only 52.5% of the patients showed normal EF. Majority of the patients were diagnosed with Hypertension. So, it follows that majority of the drugs given to the patients were also Anti Hypertensive (16%).

Upon assessment of dose of nephrotoxic drugs given to the WRF patients, no error in dose adjustment was seen as dosage was adjusted based on the creatinine clearance in them. The most common interacting drugs were identified as Atorvastatin vs Pantoprazole (25.80 %) and Ceftriaxone vs Furosemide (16.12 %). Atorvastatin related rhabdomyolysis precipitated by pantoprazole can lead to acute renal failure [10]; and ceftriaxone may cause nephrolithiasis which can be aggravated by administering it with furosemide [11].

Intuitively, hemodynamic abnormalities, such as hypotension or low cardiac output, might be expected to play a role in WRF [12]. However, hypotension was uncommon in this population, and, in fact, it was hypertension that emerged as a risk factor of WRF. A similar inference has been seen in other studies [13].

In the study by Daniel et al [14] 27% of the population showed WRF, while in our study 29.5% show WRF. In these WRF patients, Aspirin and Clopidogrel, two nephrotoxic drugs were prescribed during both therapy and discharge. They act by interstitial nephritis and Thrombotic microangiopathy respectively and can damage the

kidney [15]. Notably, age was not associated with WRF in this study population, indicating that age-related systemic effects are not specifically related to the onset of WRF.

Furthermore, Shagun S et al [16] in their study showed that renal dysfunction is strongly associated with an increased risk of adverse outcome in CVD patients. Two known nephrotoxic agents as well as two drug interactions that can precipitate WRF have been identified [10, 11]. Also, out of the 61 patients studied, hypertension was shown by 61% of the WRF population. So, Hypertension was concluded to be a risk factor for WRF.

Thus, with the worsening of renal function, the prognosis of these CVD patients will also be poor. [16-19] 30% of total population shows poor and 70% of the population show good prognosis. Although it is recognized that renal function may be more accurately assessed using calculated creatinine clearance, it is also relevant that 24-h urine collection is more cumbersome and costly and lends itself less readily to serial measurement. A strength of this investigation is that the simpler and more readily available measurement of serum creatinine provides a powerful tool for predicting adverse outcomes. The previous report by Weinfeld et al [20] studying renal function and HF highlights these methodological differences. Those investigators used creatinine clearance rates as well as serum creatinine to assess renal performance among HF patients. Patients with reduced creatinine clearance rates were more likely to develop aggravated renal deterioration and poor outcomes despite similar baseline creatinine level. Nonetheless, our study provides firm support for using increases in serum creatinine to predict adverse outcomes regardless of "actual" renal function. Furthermore, serum creatinine levels are less expensive than assessments of creatinine clearance, and they are more clinically useful for monitoring short-term fluctuations in renal function.

Whether 0.3 mg/dl increases in serum creatinine is the best gradation of renal deterioration is also controversial. Some investigators have used a rise in serum creatinine above a threshold to define renal insufficiency (e.g., creatinine >2.5 mg/dl) or a percentage increase from baseline (e.g., >25% increase), or a combination of these factors[20]. In the current investigation, we utilized a predetermined definition of an increase in creatinine >0.3 mg/dl from admission based on observations in prior studies [9, 21, 22]. Notably, this definition of WRF enables us to show that WRF is associated with adverse outcomes even in subjects whose peak serum creatinine was <2.5 mg/dl.

CONCLUSION

This study demonstrates that WRF occurs frequently in hospitalized cardiovascular patients. After assessing the demographic and baseline data obtained, it was found that 29.5% of the patients developed WRF with only two drugs and two drug interactions having any probable contribution to WRF in CVD patients.

After analysis of various factors including demographics, medical history, admission characteristics and lab values, hypertension can be concluded to be a major risk factor for WRF. Furthermore, based on the two nephrotoxic drugs and 2 drug interactions, which can precipitate WRF; and on the basis of hypertension as a parameter, we can conclude that 30% of the study population show poor prognosis while 70% show good prognosis.

Additional research is required to better delineate in-hospital factors that may precipitate WRF. Furthermore, it will be important to determine whether WRF is itself the cause of increased morbidity and mortality in these patients and, therefore, a potential target for intervention, or if WRF is simply a marker of patients with more severe pathophysiologic derangements.

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