ISSN : 2347-2251

# Indo-American Journal of Pharma and Bio Sciences

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www.iajpb.com

*Indo-Am. I. Pharm & Bio. Sc., 2022*

*ISSN 2347-2251 www.iajpb.com*

*Vol. 17, Issuse 3, Sep 2019*

Indo-American Journal of Pharma and Bio Sciences

# Loop Diuretic Use in Patients with Acute Diagnosis of Heart Failure or Left Ventricular Heart Failure: A Retrospective Analysis of Adverse Events and Complications

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## ABSTRACT

This research was deemed noteworthy since the occurrence of adverse events linked to the use of loop diuretics is on the rise per individual. The purpose of this research was to examine the potential side effects of loop diuretics used to treat patients with acute heart failure or left ventricular failure (ADHF/LVF), including arrhythmia, hyponatremia, and renal impairment. The research was planned at the tertiary care hospital's cardiology and nephrology departments and is a single-center retrospective observational study. We gathered information from the patients' medical records. After that, the findings were obtained and adjusted using statistical analysis and detailed analysis. The most significant side effects were low potassium and sodium levels, as well as renal failure and cardiac dysregulation. There were 97 cases of arrhythmia (38.04% of the total), 115 cases of hyponatremia (45.10%), and 43 cases of acute kidney injury (16.86%) related to the adverse event. To name a few examples of diuretic-related adverse medication reactions: allergic rashes, stomach pain, swelling, nausea, vomiting, diarrhea, constipation, muscular spasms, and restlessness. After stomach pain (five cases, or 12.20%), allergic rashes (24 cases, or 58.54% of the total) were the most prevalent side effect. The research found that patients with heart failure who used non-potassium sparing diuretics were more likely to die from adverse events, whereas those who took potassium supplements had better results.

**Keywords:** Side effects, Problems, Diabetes mellitus type 2, heart failure patients, low potassium levels, loop diuretics.

## INTRODUCTION

About half of the heart failure patients show signs of non-sustained ventricular tachycardia, and the majority of them have increased ventricular ectopy. Half of all cardiac fatalities occur suddenly and unexpectedly, most often as a result of arrhythmias. Hypokalemia is common in survivors of sudden cardiac death and is associated with a significantly lower level of myocardial K+ compared to controls. Patients with HF who use diuretics that do not spare potassium have an increased risk of death from any cause and cardiac complications. Use of non-K+-sparing diuretics is independently and strongly correlated with the occurrence of arrhythmia-related deaths. In addition, digoxin toxicity may occur in patients with hypokalemia because the medication is more likely to be bound to the heart muscle and renal clearance is decreased. As a result, ventricular arrhythmias and enhanced automaticity are brought about. In both animal and human models, diastolic dysfunction is worsened by K+ depletion.1 Arrhythmias such ventricular fibrillation (VF), ventricular ectopy, Torsades de Pointes (TDP), and polymorphic VT may be precipitated by hypokalemia. Evidence suggests that functional re-entry circuits are established by hypokalemia-induced changes in conduction and variability in action potential duration (APD) across regions. By decreasing the cardiac repolarization reserve and increasing intracellular Ca2+ in cardiomyocytes, hypokalemia also enhances induced arrhythmias.2

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Hyponatremia is another side effect of loop diuretics; its incidence in acute hospital settings is between 4 and 45 percent.Hyponatremia, which affects 19% to 25% of ADHF patients, stands alone as a risk factor for increased mortality and morbidity in the short and long term. Patients with ADHF are more likely to die while hospitalized and after discharge if they have even moderate hyponatremia, regardless of ventricular function. They are also more likely to need longer hospital stays and more frequent readmissions.3

Comorbid conditions are common in people with ADHF, and renal dysfunction is one of them. Similarly, temporary elevations in creatinine in the context of acute HF are not predictive of prognosis, ADHF/LVF.

but continued decline does signal irreparable damage, which foretells a poorer prognosis. Congestion also has a major impact on how renal function declines over time, and when coupled with WRF, it is a strong clinical predictor of outcome for heart failure patients.4 Acute decompensated heart failure, diuretic resistance, and deteriorating renal function are symptoms of cardiorenal dysregulation.5

There are many subtypes of cardiorenal syndrome, as shown in Table 1.
The study's goal was to learn more about the adverse effect profile of loop diuretics used to treat and to keep an eye out for other related issues such arrhythmia, hyponatremia, and renal failure.

**Table 1: Shows the subcategories of cardiorenalsyndrome.**

| Type | Denomination | Description | Example |
|---|---|---|---|
| 1 | Acute CardiorenalSyndrome | HF Leading to AKI | ACS Leading toAHF and ARF |
| 2 | Chronic CardiorenalSyndrome | CHF Leading toKidney Failure | CHF |
| 3 | Acute Nephrocardiac | AKI Leading toAHF | Uremic Cardiomyopathy,AKI Related |
| 4 | Chronic Nephrocardiac | CKD Leading toHF | LVH and Diastolic HF dueto RF |
| 5 | Secondary | Systemic Disease Leading to Heart and Kidney Failure | DM, Vasculitisand Sepsis |

## MATERIALS AND METHODS

### Study Design

A Single-Centered, Retrospective Observational Study.

***Study Site***

The study was carried out in the Cardiology and Nephrology Departments of one of the Tertiary Health- Care Centre in South-India, CARITAS HOSPITAL, located in Thellakom, Kottayam. It is a multi-specialty hospital with modern technology, automated equipments and the first quaternary care hospital in Kerala to achieve the coveted JCI (Joint Commission International). Caritashas also won the NABH accreditation. The hospital has an in-patient capacity of 670 beds and has 24-hr emergency and accident trauma care facilities.

### Study Period

The study was carried out for a period of 36 months (3 years), starting from November 2017 to November2020.

### Sample Size

The adequate sample size required to support the study was calculated by using the ready-made table. The table was used to calculate the sample size by taking relative precision ($\in$ = 10% / 0.10) and 95% confidence interval.

Sample size Determination = 100(1- et)%

Relative precision = 10%

Confidence level = 95%

Equation n = (1- $\alpha/2$) $\div \in$

[RP = 0.10 and a confidence level of 95% a sample

ISSN 2347-2251 www.iajpb.com
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size
of 385.]

### Study Population

The data of all in-patients who visited the hospital in the time period (November 2017-November 2020, respectively) regardless of age and sex in Cardiology ICU and who satisfied the inclusion and exclusion criteria wereincluded in the study.

The inclusion criteria for the study were:

- Patients administered with loop diuretics.
- Patients with an age group greater than 20

years.The exclusion criteria for the study were as follows:

- Patients administered with the drugs that affect thebaseline K+ like ARBs, ACE Inhibitors.
- Patients with malignancy, chronic liver disease, cardiogenic blocks.
- Patients whose follow-up details were missing.

## MATERIALS AND METHODS

Notable clinical laboratory parameters included blood urea, serum creatinine, and electrolyte levels of potassium and sodium both before and after diuretic treatment, as well as the patient's age, gender, comorbidities, social history, and length of hospital stay. Vital signs and medical history were also documented. The electrolyte panel, electrocardiogram report, and renal function test were used to record, evaluate, and interpret the incidence of further adverse events such as hyponatremia, cardiac conduction abnormalities (such as arrhythmia), and deteriorating renal function.

## RESULTS

### Monitoring the Other Associated Complications inADHF/LVF Patients

During the study, it was observed that complications like Arrhythmia, Hyponatremia and Acute Kidney Injury (AKI) in patients with ADHF/LVF (Table 2). Diuretic- induced electrolyte disturbances may result in fatal Arrhythmias in patients with ADHF/LVF. Hyponatremia is an occasional, but serious, and potentially fatal complication of diuretic therapy. AKI is a sudden decline in kidney function, associated with a range ofadverse outcomes, particularly an increase in subsequent admission with heart failure. In a total of 170 patients, apart from hypokalemia complications like arrhythmia occurred in 97 patients (38.04%), 115 patients (45.10%) resulted in hyponatremia, and acute kidney injury has occurred in 43(16.86%) of patients and it was depicted in Figure 1.

### Evaluation of Hyponatremia

#### *Severity of Hyponatremia*

Based on the findings, Hyponatremia also occurred in patients administered with loop diuretics in addition to hypokalemia. Out of 170 patients who had hypokalemia, 55 (32.35%) patients had a normal serum sodium level. Upon analyzing the severity, the majority of patients

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Vol. 17, Issuse 3, Sep 2019
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**Table 2: Shows the Determination of other Complications along with Hypokalemia.**

| Complications | *n* = 255 | Percentage (%) |
|---|---|---|
| Hyponatremia | 115 | 45.10% |
| Arrhythmia | 97 | 38.04% |
| Acute Kidney Injury | 43 | 16.86% |

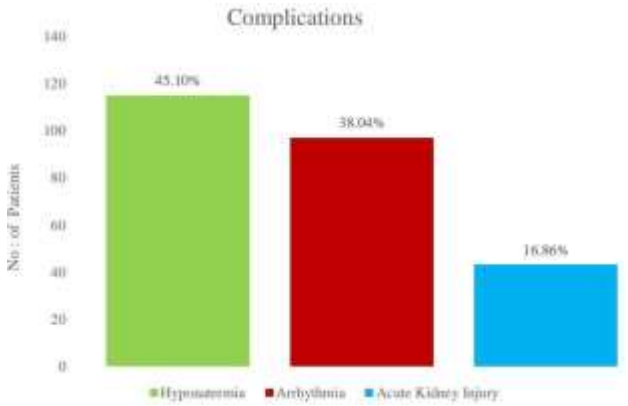


**Figure 1: The Figure below shows the other associated compli-cations along with hypokalemia.**

**Table 3: Depicts the Details of Hyponatremia Occurred in Patients.**

| Classifications | *n*=170 | Percentage (%) |
|---|---|---|
| Normal | 55 | 32.35% |
| Mild | 65 | 38.23% |
| Moderate | 43 | 25.29% |
| Severe | 7 | 4.11% |

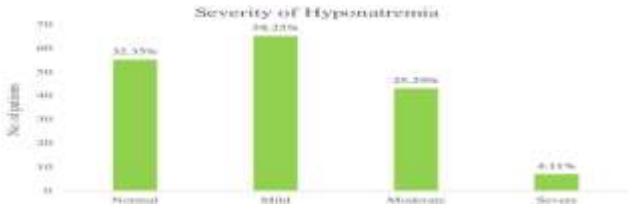


**Figure 2: Depicts the Details of Hyponatremia Occurred in Patients.**

65 (38.23%) resulted in mild hyponatremia along with 43(25.29%) patients moderate, and 7(4.11%) had severe Hyponatremia (Table 3, Figure 2).

### Management of Hyponatremia

Out of a total of 115 patients (45.10%) with Hyponatremia, 44 patients (38.26%) patients were managed with various therapeutic interventions, and 71 patients (61.67%) werenot managed which is depicited in Table 4.

### Various Treatment Strategies for the Managementof Hyponatremia

Out of 115 patients with Hyponatremia, 44 patients were managed with therapeutic interventions. Various

| Table 4: Describes the Management of Hyponatremia. | | |
|---|---|---|
| **Interventions** | ***n*= 115** | **Percentage (%)** |
| Not Treated | 71 | 61.67% |
| Treated | 44 | 38.26% |

| Table 5: Demonstrates the Incidence of various Arrhythmic Events. | | |
|---|---|---|
| **Arrhythmic Events** | ***n*= 97** | **Percentage (%)** |
| Atrial Fibrillation | 15 | 15.46% |
| Heart Block | 19 | 19.59% |
| Sinus Bradycardia | 11 | 11.34% |
| Sinus Tachycardia | 38 | 39.17% |
| Ventricular Fibrillation | 8 | 8.25% |
| Ventricular Tachycardia | 6 | 6.19% |

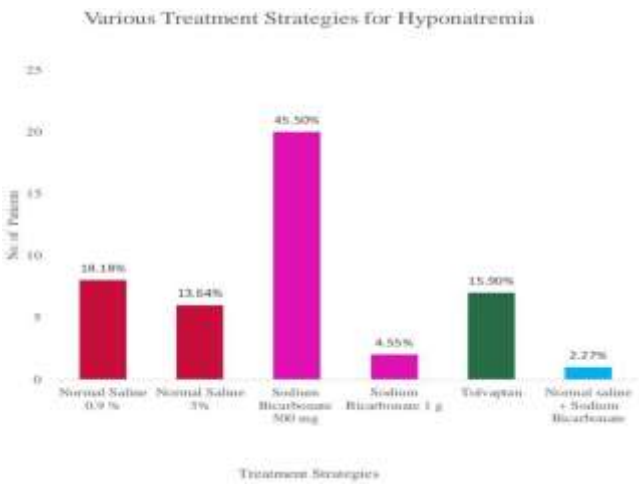


**Figure 3: Shows the Various Treatment Strategies Provided forthe Management of Hyponatremia.**

treatment strategies provided were Normal Saline (NS), Sodium bicarbonate, Tolvaptan, a combination of Normal Saline and Sodium Bicarbonate. From a totalof 44 (38.26%) patients with Hyponatremia, Sodium Bicarbonate was given to 22 patients as 500mg (20, 45.45%) patients, and 1g (2, 4.55%) patients respectivelyand it was clear from Figure 3.

### Classifications of Arrhythmic Events

From Table 5 and Figure 4, it was evident that among the various Arrhythmic Events, Sinus Tachycardia is themajor Arrhythmic event observed in 38 patients (39.17%). Heart block was present in 19 patients (19.59%). Atrial Fibrillation was occurred in 15 patients (15.46%). Apart from these arrhythmic events, Sinus bradycardia was present in 11 patients (11.34%). Ventricular fiibrillation occurred in 8 patients (8.25%). Ventricular Tachycardia was present in 6 patients (6.19%).

### Side Effect Profile of Loop Diuretics used in the Treatment of ADHF/LVF

### Adverse Drug Reaction Profile of Loop Diuretics

Based on the understanding, the adverse events occurred in 41 (24.11%) patients (Table 6, Figure 5).

### Details of ADR

Based on the findings, the adverse drug reactions as aresult of diuretic use can be classified as allergic rashes,

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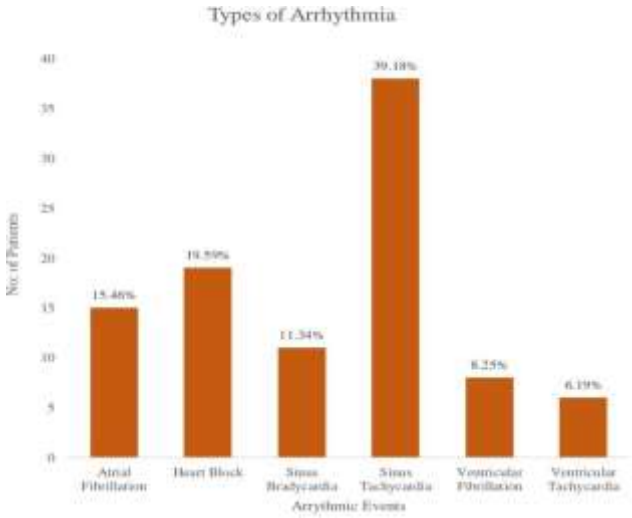


**Figure 4: Demonstrates the Incidence of Various ArrhythmicEvents.**

**Table 6: Illustrates the Adverse Drug Reaction Profile of Loop Diuretics.**

| No. of Patients | *n*= 170 | Percentage (%) |
|---|---|---|
| With ADR | 41 | 24.11% |
| Without ADR | 129 | 75.88% |

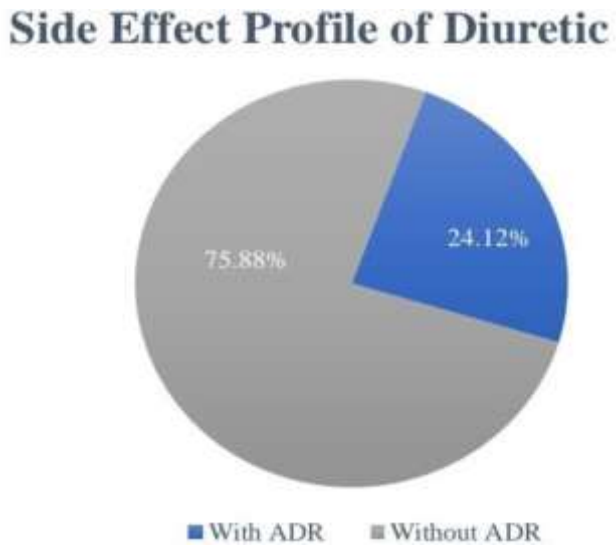


**Figure 5: Illustrates the Adverse Drug Reaction Profile of Loop Diuretics.**

| Table 7: Describes the Details of Different ADRs. | | |
|---|---|---|
| **Details of ADR** | ***n* = 41** | **Percentage (%)** |
| Allergic Rashes | 24 | 58.54% |
| Abdominal Discomfort | 5 | 12.20% |
| Edema | 4 | 9.76% |
| Vomiting | 3 | 7.32% |
| Diarrhoea | 2 | 4.88% |
| Constipation | 1 | 2.44% |
| Muscle Spasm | 1 | 2.44% |
| Restlessness | 1 | 2.44% |

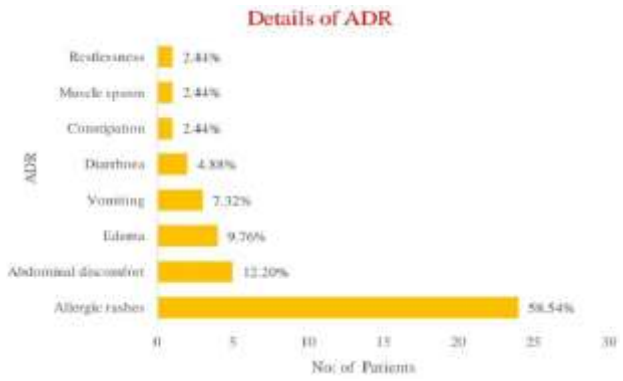


**Figure 6: Describes the Details of ADRs.**

abdominal discomfort, edema, vomiting, diarrhoea, constipation, muscle spasm, restlessness (Table 7). The most common adverse event observed was allergic rashes 24 (58.54%) followed by abdominal discomfort 5 (12.20%) and it was clear from Figure 6.

## DISCUSSION

### Complications

Acute renal damage, arrhythmia, and hyponatremia were the main problems that occurred. Hyponatremia during hospitalization may worsen the situation for HF patients. This is indicative of a worse prognosis due to hyponatremia, which in turn increases the risk of in-hospital morbidity, mortality, and length of hospital stay. Hyponatremia may also be linked to a number of medical issues and risk factors for cardiovascular disease, including diabetes mellitus, COPD, and alcohol use. Hyponatremia in heart failure patients may be caused by high dosages of furosemide and spironolactone or the use of both diuretics simultaneously, according to a similar research by Velat Ivan et al.6. This is especially true when combined with other risk factors such advanced age, diabetes, and alcohol use. It is possible that reducing the dosage of diuretics may assist these individuals avoid hyponatremia, which would improve their clinical condition and prognosis. Similar to what Velat Ivan et al. found, we also found... Most of them had mild hyponatremia, which was treated with sodium bicarbonate, according to the evaluation of hyponatremia severity. Potassium supplementation improved outcomes in heart failure patients, but non-potassium sparing diuretics increased the chance of arrhythmic death, according to a comparable research by Hoss et al.,7. These findings corroborated those of this investigation. Mehta et al.8 found that patients using diuretics were less likely to have their kidney function restored. According to the latest SPARK trial by Bagshaw et al.9, furosemide does not stop AKI from becoming worse or decrease the need for renal replacement treatment. All of these results lined up with what the research found.

### Side Effect Profile of The Drugs

In the comparison of Furosemide with Torsemide, it was recognized that the incidence of ADR remained high with Furosemide. In particular, these were allergic rashes 24(58.54%) followed by skin reactions, GI disturbances, electrolyte abnormalities, *et al.*[10] conducted a similar study and the results were inconsistent with the findings of the study for the reason that there was no difference in the

ISSN 2347-2251 www.iajpb.com
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medication side-effects.

## CONCLUSION

Hypokalemia is more common in heart failure patients, according to the research. A small but growing body of research suggests that keeping blood potassium levels over 4.0 mmol/l may reduce the likelihood of sudden cardiac death. Keeping blood potassium levels within the normal range may help reduce the risk of potentially fatal arrhythmias, such as ventricular arrhythmias, and keep electrocardiogram readings stable. Independent predictors of deteriorating outcomes included confounding variables such as age, diabetes mellitus (DM), hypertension (HTN), and the development of acute kidney injury (AKI) in relation to potassium levels. However, whether or not hypokalemia really worsens AKI is still up for debate. To reduce the risk of hypokalemia, individuals with symptomatic HF (NYHA class III-IV) should take the lowest effective dosage of diuretic. Aldosterone receptor antagonists, like Spironolactone, may treat mild hypokalemia. This research sheds light on the adverse effect profile of loop diuretics used to treat ADHF/LVF patients, as well as the risks associated with these drugs, such as arrhythmia, hyponatremia, and renal impairment.

## ACKNOWLEDGEMENT

The authors would like to thank the physician of Department of Nephrology, Caritas Hospital, Kottayam

for this grateful support. We are proudly grateful to Mr. Jobin Kunjunom Vilapurathu, Assistant ProfessorDepartment of Pharmacy Practice, Nirmala College of Pharmacy, Muvattupuzha for his valuable guidance and support.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ADHF/LVF:** Acute Decompensated Heart Failure/ Left Ventricular Heart Failure; **HF:** Heart Failure; **TDS:** Torsades-de Pointes; **VF:** Ventricular Fibrillation; **APD:** Action Potential Duration; **CHF:** Congestive Heart Failure; **AKI:** Acute Kidney Injury; **ADR:** Adverse DrugReaction.

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