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FREQUENCY OF USE OF RAAS INHIBITORS IN PATIENTS WITH HFrEF AT A TERTIARY CARE HOSPITAL.

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Abstract: **Background:** Objective: To determine the frequency of use of RAAS inhibitors in patients with HFrEF at a tertiary care hospital. **Methods:** This cross-sectional study was done at the outpatient cardiology department of a tertiary care cardiac center located in Karachi within a six-month period following ethical approval. Non-probability consecutive sampling was used to enroll a total of 113 heart failure with reduced ejection fraction (HFrEF) patients aged 2065 years. Severely adverse reacting patients to RAAS inhibitors or end-stage renal disease were not included. A structured proforma was used to obtain baseline demographic and clinical data. The SPSS v26 was used to analyze data. Quantitative variables were given as the mean plus SD or median (IQR) and qualitative variables as frequencies and percentages. The effect modifiers were controlled by applying stratification and a chi-square or Fisher exact test was used to compare the two. **Results:** The study involved 113 patients with HFrEF. The mean age was 41.67 years with a standard deviation of 13.44 years, and 77 (68.1%) participants were males. It was established that a total of 45 (39.8%) patients had diabetes mellitus and 73 (64.6%) had hypertension. A total of 79 (69.9%) patients received RAAS inhibitors, and 34 (30.1%) patients did not. Among RAAS inhibitor users, angiotensin receptor blockers were the most prescribed (35; 44.3%), followed by ACE inhibitors (29; 36.7%), and aldosterone antagonists (15; 19.0%). The bivariate analysis revealed that the relationship between hypertension and the use of RAAS inhibitors is statistically significant ($p = 0.011$), but no statistically significant relationship was found between other demographic and clinical variables and RAAS inhibitor use. **Conclusion:** Approximately 69.9% of HFrEF patients were receiving RAAS inhibitor therapy. Even though the general utilization was moderate, a substantial proportion of patients (30.1%) were not receiving guideline-based treatment, which suggests a necessity for better implementation of evidence-based approaches in heart failure management.

Keywords: #HFrEF #HeartFailure #RAASinhibitors

INTRODUCTION

The activation of neurohormones is a characteristic of heart failure. In spite of the fact that the retention of fluid and the consequent strain in the myocardium are gradual with the stimulation of the natriuretic peptide (NP) system, cardiac failure leads to the stimulation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone (RAAS). NP results in diuretic effects and vasodilatory effects, as compared to the RAAS and SNS, which lead to vasoconstriction and fluid retention. These two systems act in opposition, driving a neurohormonal imbalance that is central to the pathophysiology of heart failure.

Heart failure patients may be categorized into three phenotypes, including HF with preserved ejection fraction (HFpEF) (LVEF ≥50%), HF with mid-range ejection fraction (HFmrEF) (LVEF 4049%), and HF with reduced ejection fraction (HFrEF) (LVEF <40%), based on their left ventricular ejection fraction (LVEF) on imaging. [1] Nevertheless, each phenotype has SNS and RAAS activity and detectable NP levels. [2]
Among the most significant advances of modern medicine is the use of medications that inhibit the RAAS and the SNS to treat individuals with HFrEF; a more recent one is sacubitril-valsartan, studied in the PARADIGM-HF study [3]. [4]

Sacubitril-valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) that combines the angiotensin receptor blocker (ARB) valsartan with the neprilysin inhibitor sacubitril. [5]. The aim of this study is also to describe the mechanisms underlying the beneficial effects of sacubitril-valsartan in HFrEF patients and to explore its potential future applicability in the broader management of heart failure. These hormones are known as natriuretic peptides (NPs), and they are produced in the form of pro-peptides and are stored in myocyte granules. The majority of them include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). [6]. Transmembrane receptors (NPRs) mediate the biological effects when the biological effects of the breakdown of pro-peptides (furin in case of BNP and corin in case of ANP) in response to myocardial strain (high intracardiac pressure or volume or both) occurs. A causes improved glomerular filtration, vasodilation, greater renal water and salt excretion, and less production of renin and aldosterone through intracellular signalling cascades, increased intracellular second messenger activity of cyclic guanosine monophosphate (cGMP) attached to NPR.

A study by Seung Hun Lee et al. has shown that 544 (74.9) of the RAASi treatment group continued taking RAASi at 12 months [Maintain-RAASi group], 108 (14.8) were dropped, and the remaining 74 (10.19) did not take it. [9]. A different study by Evangelos Kanonidis reported the prescriptions of 1290 individuals to RAS inhibitors: 314 (24.34) individuals. [10].
The argument behind examining the prevalence of RAAS inhibitor use in HFrEF patients in the hospital is the clinical utility of such drugs as the first line of treatment in the management of HFrEF, with the evidence-based guidelines strong support. Although they have been proven to be effective, underutilization is a problem of concern that can affect the outcome of patients. Follow-up of the patients regarding the use of RAAS inhibitors is important to measure compliance with recommendations, quality of care, and to be able to see where improvement is possible in managing patients. It also directs research and educational efforts to streamline the HFrEF treatment plans.

METHODOLOGY

It was a cross-sectional study carried out at the Department of Outpatient Cardiology, National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan, during six months after the institutional review board and the College of Physicians and Surgeons, Pakistan, had approved the research synopsis.

Patients of both genders and aged between 20 and 65 years who fulfill the operational definition of heart failure with reduced ejection fraction (HFrEF), as outlined in the study protocol, were eligible. The sample size (n = 113) was determined with the help of the WHO sample size calculator based on the expected prevalence rate of 74.9, 95% confidence interval, and 8% margin of error. A non-probability consecutive sampling technique was used in recruiting patients.

Inclusion and Exclusion Criteria.

Inclusion criteria:
HFrEF patients between 20 and 65 years old of either sex who consented to take part in the study by signing a written informed consent.

Exclusion criteria:
Patients who had a history of severe adverse reactions to RAAS inhibitors (e.g., angioedema or drug-induced renal dysfunction), those with end-stage renal disease (who received renal replacement therapy (hemodialysis or peritoneal dialysis)), were excluded to minimize confounding and to assess chronic management, which was steady.
The principal investigator identified and recruited eligible patients. Informed consent was taken by

written means before enrolment. They were also made to take baseline demographic and clinical data such as age, gender, residence, body mass index (BMI), heart failure duration, diabetes mellitus, hypertension, smoking status, and family history of heart disease using a predesigned structured proforma. All the patients were handled per the standard institutional management of heart failure. The operational definitions used in the study protocol on RAAS inhibitors and the type of RAAS inhibitor prescribed were used to assess the use of RAAS inhibitors and the type of RAAS inhibitor prescribed. The principal investigator conducted data collection under the guidance of a consultant cardiologist having a clinical experience of over five years after the completion of the fellowship.

SPSS version 26.0 was used in analyzing data. The quantitative variables (age, height, weight, BMI, period of the disease) were shown as the mean value with the standard deviation or as the median with the interquartile range, which were tested by the Shapiro-Wilk test for data normality. The qualitative variables (age groups, gender, residence, diabetes, hypertension, smoking status, family history of heart disease, RAAS inhibitor use and type of RAAS inhibitor) were reported as frequencies and percentages. Stratification was used in controlling effect modifiers. Chi-square or Fisher's exact tests (as appropriate) were used to do the post-stratification comparisons. The p-value was taken as significant at a 0.05 level.

RESULTS

The study enrolled 113 patients having heart failure with reduced ejection fraction (HFrEF). The average age of the respondents was 41.67 ± 13.44 years. The mean height and weight were 168.07 ± 7.36 cm and 78.42 ± 12.18 kg, respectively, and this resulted in the mean body mass index (BMI) equal to 27.90 ± 4.83 kg/m 2. The mean duration of the disease was 17.61 months with a standard deviation of 9.48 months. (Table I).

Concerning the age, 59 (52.2%) patients fell within the age category of 40 to 65 years, and 54 (47.8%) patients fell within the age category of 20 to 40 years. Most of the respondents were men (77; 68.1%), while 36 patients (31.9%) were women. Most of them lived in urban areas (62; 54.9%), and 51 patients (45.1%) lived in rural locations. There were comorbidities prevalent in 45 patients having diabetes mellitus (39.8%) and 73 patients having hypertension (64.6%). The prevalence of the smoking risk was reported in 30 patients (26.5%), and positive family history of heart disease in 34 patients (30.1%) (Table II).

Concerning the RAAS inhibitor therapy, 79 (69.9%) patients were on the RAAS inhibitors, and 34 (30.1%) patients were not. Among RAAS inhibitor users (n=79), angiotensin II receptor blockers (ARBs) were the most frequently prescribed (35; 44.3%), followed by angiotensin-converting enzyme (ACE) inhibitors (29; 36.7%), and aldosterone antagonists (15; 19.0%). Patients who did not take RAAS inhibitors (34; 30.1%) were considered not applicable to the analysis of the RAAS type (Table III).

The results of bivariate analysis indicated no statistically significant relationship between using RAAS inhibitors and age (p = 0.919), gender (p = 0.420), weight (BMI) (p = 0.214), duration of HFrEF (p = 0.988), living status (residence) (p = 0.495), diabetes mellitus (p = 0.821), smoking status (p = 0.359), and having a heart disease-positive family history (p = 0.918). Nevertheless, hypertension was significantly associated with the use of RAAS inhibitors (p = 0.011), which means that hypertensive patients were more likely to receive RAAS inhibitor therapy (Table IV).

Table I: Mean & SD of Age, height, weight, BMI & Duration of disease. (n = 113)

Variables	Mean	Standard Deviation
Age (Years)	41.67	13.44
Height (cm)	168.07	7.36
Weight (kg)	78.42	12.18
BMI	27.90	4.83
Duration of disease	17.61	9.48

Table II: distribution of Age, Gender, residence, DM, HTN, Smoking & Family history of heart disease. (n = 113)

Variables		Frequency	Percent
Age	20 – 40 Years	54	47.8
	40 – 65 Years	59	52.2
Gender	Male	77	68.1
	Female	36	31.9
Residence	Urban	62	54.9
	Rural	51	45.1
Diabetes	No	68	60.2
	Yes	45	39.8
Hypertension	No	40	35.4
	Yes	73	64.6
Smoking	No	83	73.5
	Yes	30	26.5
Family history of Heart Disease	No	79	69.9
	Yes	34	30.1
	Total	113	100.0

Table III: Frequency of Use of RAAS Inhibitors in Patients with HFrEF at a Tertiary Care Hospital. (n = 113).

RAAS Use	Frequency	Percent
No	34	30.1
Yes	79	69.9
RAAS Type		
Not Applicable	34	30.1
ACE Inhibitor	29	25.7
ARB	35	31.0
Aldosterone Antagonist	15	13.3
Total	**113**	**100.0**

Table IV: stratification of RAAS Use with age, Gender, BMI, Duration of disease, residence, DM, HTN, Smoking & Family history of heart disease. (n = 113).

Variables		**RAAS Use**		**P - Value**
		No	**No**	
Age	20 – 40 Years	16	38	0.919
	40 – 65 Years	18	41	
Gender	Male	25	52	0.420
	Female	9	27	
BMI	Normal	1	0	0.214
	Overweight	11	20	
	Obese	22	59	
Duration of Hfref	≤ 12 months	12	28	0.988
	> 12 months	22	51	
Residence	Urban	17	45	0.495
	Rural	17	34	
Diabetes	No	21	47	0.821
	Yes	13	32	
Hypertension	No	18	22	0.011

	Yes	**16**	**57**	
Smoking	**No**	**23**	**60**	**0.359**
	Yes	**11**	**19**	
Family history of heart disease	**No**	**24**	**55**	**0.918**
	Yes	**10**	**24**	
TOTAL		**34**	**79**	**113**

DISCUSSION

In this cross-sectional, descriptive study of 113 patients with heart failure with reduced ejection fraction (HFrEF), about 69.9% were prescribed a RAAS inhibitor, which is a moderate level of guideline-based medical therapy in a tertiary care environment. In spite of the high recommendation of RAAS inhibitors in HFrEF following the established advantages in the morbidity and mortality reduction, the actual prescription rates diffuse across geographic areas and care environments because of numerous clinical and system-level influences [11,12].

Angiotensin converting enzyme (ACE) and angiotensin II receptor blockers (ARB), as well as mineralocorticoid receptor antagonists (MRA), are the basic pillars of HFrEF management. These medications have the opposite effect on the pathologic neurohormonal stimulation, which causes reversal of the negative cardiac remodelling and enhances survival [11,12]. Numerous real-world studies demonstrate suboptimal utilization of RAAS inhibitors and adjunct therapies, despite strong evidence from landmark clinical trials, largely driven by concerns over adverse reactions (e.g., hypotension, hyperkalemia, and renal dysfunction), patient comorbidities, and challenges in dose titration and access [11,13].

The high correlation between hypertension and RAAS inhibitor usage in the current research ($p = 0.011$) indicates a trend in clinical practice according to which patients with high blood pressure are more likely to take RAAS blockers as they are cardioprotective and antihypertensive agents. This result is consistent with information that indicates that the clinical characteristics tend to affect treatment choice and compliance with guideline recommendations [11,14].

Comparative international data indicate that there is a relatively high prevalence of RAAS inhibitor use in most parts of the world, but still high regional differences. As an example, a systematic review and meta-analysis found that the prevalence of the use of renin-angiotensin system inhibitors among HFrEF patients was approximately 82%, yet it varied significantly across high-income and low-income countries [14]. Even higher adherence to guideline-based therapies such as RAAS inhibitors, MRAs, and newer agents such as angiotensin receptor-neprilysin Inhibitors (ARNIs) have been linked to integration of multidisciplinary care programs in heart failure, although achievement of targeted dosage has been a challenge in some specialized care centers [14].

Although the advantages of RAAS inhibitor treatment are obvious, a significant number of eligible patients worldwide never get the best doses of medications endorsed by the guidelines [11,14]. The obstacles to prescribing are physician fears of adverse effects, patient intolerance and competing comorbidities such as chronic kidney disease or hypotension, which usually restrict dose increases and chronic therapy. Interventions such as clinical decision support tools and structured follow-up programmes have demonstrated efficacy in improving adherence to evidence-based therapies in heart failure cohorts and should be considered in settings with similar gaps in guideline compliance [14, 15].

This research is limited in a number of ways. The cross-sectional nature of the study does not allow causal implications about long-term effects of using RAAS inhibitors, and non-use was not captured in a systematic way (e.g. adverse events, renal impairment). Also, a single-center environment might restrict the applicability of the results to more general populations. However, the findings are relevant to real-world medication utilization rates in HFrEF and the necessity of continuous work to maximize adherence to evidence-based guidelines.

CONCLUSION

The frequency of RAAS inhibitor use in this cross-sectional study at a tertiary care hospital was 69.9% among patients with heart failure with reduced ejection fraction (HFrEF). Even though approximately 70% of patients were receiving guideline-recommended RAAS therapy, a substantial proportion (30.1%) were not receiving these medicines. Among RAAS inhibitor users, angiotensin receptor blockers were the most frequently prescribed (44.3%), followed by ACE inhibitors (36.7%) and aldosterone antagonists (19.0%). The use of RAAS inhibitors was significantly associated with hypertension ($p = 0.011$), and no statistically significant relationship was found between RAAS inhibitor use and other demographic or clinical factors (all $p > 0.05$). These results indicate moderate compliance with guideline-based medical therapy and emphasize the necessity of further work to optimize

evidence-based treatment in patients with HFrEF.

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