



**PRESCRIPTION OF RENIN-ANGIOTENSIN SYSTEM BLOCKERS AND RISK OF
ACUTE KIDNEY INJURY IN PATIENTS WITH DIABETES MELLITUS:
RETROSPECTIVE STUDY**

Akshitha D. Ajay¹, Gini C. Johns², Mareena Mathew^{3*}, Athira S.⁴ and Cijo George⁵

^{1,2,3}Pharm.D Interns, KVM College of Pharmacy, Kokkothamangalam, Cherthala, Kerala, India.

⁴Assistant Professor, Department of Pharmacy Practice, KVM College of Pharmacy, Kokkothamangalam, Kerala, India.

⁵Associate Professor, Department of Pharmacy Practice, KVM College of Pharmacy, Kokkothamangalam, Cherthala, Kerala, India.

***Corresponding Author: Mareena Mathew**

Pharm.D Interns, KVM College of Pharmacy, Kokkothamangalam, Cherthala, Kerala, India.

Article Received on 12/12/2022

Article Revised on 01/01/2023

Article Accepted on 22/01/2023

ABSTRACT

The development of AKI is thought to be significantly correlated with the use of ACE inhibitors and ARBs. Patients who have both hypertension and type 2 diabetes mellitus are more likely to experience renal problems than those who either have hypertension or Type 2 diabetes mellitus. A retrospective observational cohort study conducted was conducted with 200 in patients among the study subjects of the age group of 18 years and above. Majority of the cases were males (50.5%) than females (49.5%). Cockcroft-Gault-eGFR was 57.90±21.6 mL/min in the ACEI group and 24.2 mL/min in the ARB group. Average baseline creatinine(mg/dL) of non-exposed group was 1±0.82 mg/dL and exposed group was 0.96 ±0.2 mg/dL. ACEIs were administered to 1% of the patients (1/100) and ARBs to 99% (99/100). The highest incidence percentage of increased creatinine according to the ARB type was associated with the use of telmisartan 10.7% (7/65 exposed), and olmesartan 14.2% (2/14 exposed), losartan 15.38% (2/13 exposed). A total of 11 (5.5%) patients developed AKI. From a total of 200 cases, majority had stage 1 (3.5%) followed by stage 2 (2.5%) and stage 3 (1%) AKI. There was a significant association between stages of AKI and administration of ARBs/ACE -inhibitors ($\chi^2= 8.633$, $p<0.05$). Relative risk of AKI and administration of ARBs/ACE -inhibitors was found to be 5.50 ($\chi^2= 6.664$, $df= 1$, $p= 0.010^{**}$).

KEYWORDS: Angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARB), acute kidney injury (AKI), estimated glomerular filtration rate (eGFR).

INTRODUCTION

^[1]As per KIDIGO, AKI is defined as any of the following (*Not Graded*).

- Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) within 48 hours; or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours) is a common complication in hospitalized patients and has been consistently associated with increased long-term risk of death, de novo or worsening chronic kidney disease (CKD), and end-stage renal disease (ESRD).

Acute kidney injury (AKI), which is characterised by a precipitous loss in renal function, is highly related with higher mortality and longer hospital stays.

AKI stage	KDIGO	RIFLE	AKIN	Urine output
1 (R)	Increase \geq 0.3 mg/dl within 48 h or \geq 1.5- to 2-fold from baseline	Increase \times 1.5 baseline or GFR decrease $>$ 25%	$<$ 0.5 ml/kg/h for 6-12 h	Increase 1.5-1.9 times from baseline or \geq 0.3 mg/dl increase within 48 h
2 (I)	2.0-2.9 times from baseline	Increase \times 2 from baseline or GFR decreased $>$ 50%	$<$ 0.5 ml/kg/h for 12 h	Increase $>$ 2- to 3-fold from baseline
3 (F)	3.0 times from baseline or increase in serum creatinine to \geq 4.0 mg/dl or initiation of renal replacement therapy or, in patients $<$ 18 years, decrease in eGFR to $<$ 35 ml/min per 1.73 m ²	Increase \times 3 from baseline, or serum creatinine $>$ 4 mg/dl with an acute rise $>$ 0.5 mg/dl or GFR decreased $>$ 75%	$<$ 0.3 ml/kg/h for 24 h or anuria for 12 h	Increased $>$ 300% ($>$ 3-fold) from baseline, or \geq 4.0 mg/dl with an acute increase of \geq 0.5 mg/dl or on renal replacement therapy

^[2-3] A lot of people suffer with hypertension, especially after reaching middle age. Adults are considered to have normal blood pressure when their systolic and diastolic readings are between 120 and 80 mmHg.

ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) are firmly believed to be linked to the emergence of AKI, particularly during acute sickness. For a given systemic blood pressure, ACEI/ARBs preferentially vasodilate the kidney's efferent arterioles (the tiny blood arteries that leave the kidney glomeruli), which lowers renal filtration pressure. This decrease in efferent vascular tone results in decreased glomerular filtration and perhaps AKI under conditions of severe hypovolemia or hypotension (such as those caused by volume depletion in an acute illness).

The risk of AKI in patients on ACEI/ARB alone has been compared in earlier observational studies. So, our goal was to look at the relationship between AKI and the use of ACEI/ARB. Patients who have both hypertension and type 2 diabetes (T2 DM) are more likely to experience renal problems than those who either have hypertension or T2 DM.

MATERIALS AND METHOD

A retrospective study was conducted among the in-patients admitted to SH Medical Centre hospital, a tertiary care hospital in Kerala, India. The patient records admitted in cardiology, nephrology and general medicine department were collected of patients having type 2 diabetes mellitus and hypertension. Data such as

RESULT AND DISCUSSION

GENDER

Table 1

Gender	Frequency	Relative frequency (%)
MALE	101	50.5
FEMALE	99	49.5
	N=200	100

Table 1 it shows that, in our study containing a total of 200 cases majority of the patients were males (50.5%), followed by females (49.5%). Other studies^[6,9] also have the similar results.

demographic characteristics, symptoms and its duration, comorbidities, and clinical parameters like blood pressure were collected. Laboratory parameters such as serum creatinine, serum potassium, GRBS, FBS, PPBS, HbA1c were collected for both exposed and control study subjects. The data of patients having antihypertensives ACEIs and ARBs were also collected. For the determination of risk of AKI associated with ACEIs and ARBs we used KIDIGO guidelines.

This data in this study belongs to patients who have already been discharged and which was collected at the end of the treatment, so this study is not in a violation of the rights and interests of the participants and has little impact on their mental or physical health. The study was approved by the IEC of the SH Medical Centre, Kottayam. Therefore, informed consent was not required

STATICAL ANALYSIS

A retrospective study was conducted among the in-patients admitted to hospital. The data of patients having antihypertensive ACEIs and ARBs were also collected. Descriptive statistics was used to summarize variable demographic parameters and study objectives. Discrete variables were tabulated and chi square test were used to analyze it. A p value of $<$ 0.05 was considered as significant. Karl Pearson's coefficient of correlation was used to correlate Serum creatinine age, sex, duration of use, BMI, blood pressure. Chi square was used to find the association of AKI with administration of renin angiotensin system blockers.

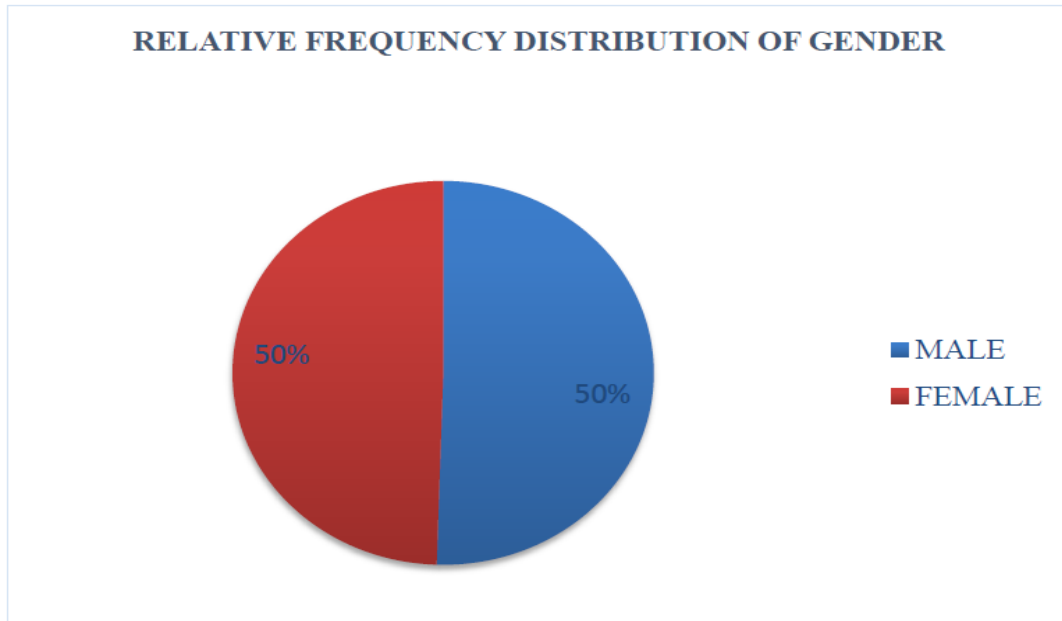


Figure 1

Table 2

Gender	Exposed	Non exposed	Total (n=200)	Relative frequency(%)
MALE	40	61	101	50.5
FEMALE	60	39	99	49.5
	100	100	200	100

Table 2 shows that out of 200 patients, 40 were male and 60 were female in exposed group and 61 were male and 39 were female in non-exposed group. The relative

frequency was found to be 50.5% for male and 49.5% for female. Other studies^[6,9] also have the similar results.

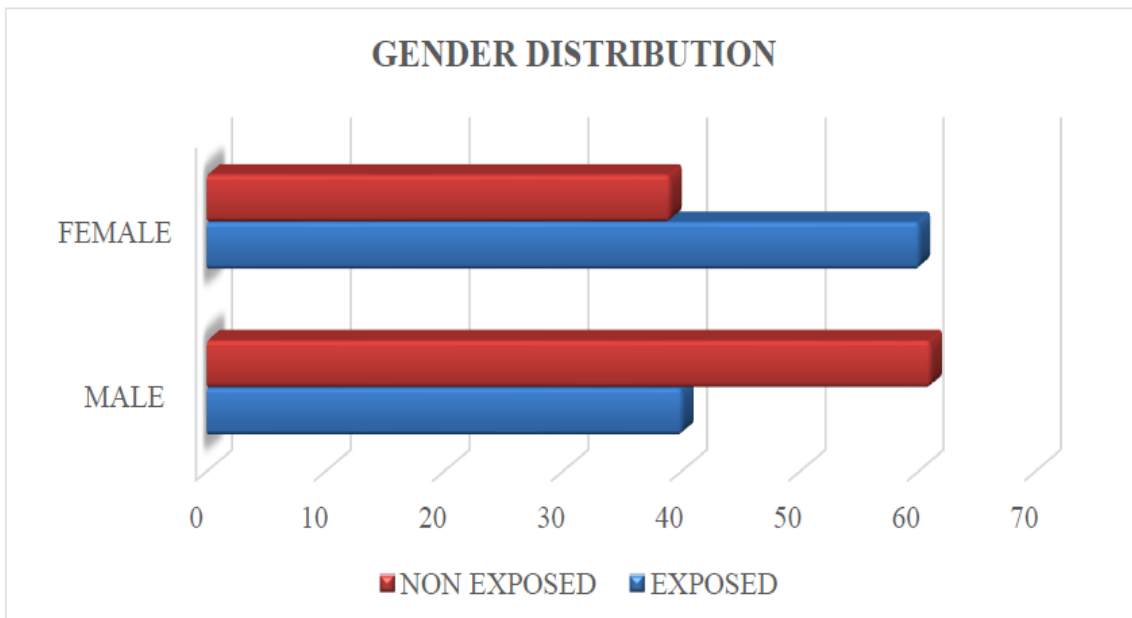


Figure 2

The gender distribution in exposed and non-exposed group is depicted in figure 2.

AGE

Table – 3

Age (n=200)	Non exposed	Exposed	Total	Relative frequency (%)
≤50	4	3	7	3.5%
51-59	21	26	47	23.5%
60-70	45	27	72	36%
71-79	14	28	42	21%
≥80	16	16	32	16%
	100	100	200	100

The average age of patients in the non-exposed group was 62 ± 13 years and 68 ± 11 years in the exposed group. The table 3 demonstrates that from a total of 100 cases, the majority of the patients (71%) were in the age

group of 60 years above, which was consistent with prior reports in the literatures.^[6,7,8,9]

Relative frequency distribution of age groups is depicted in figure 3.

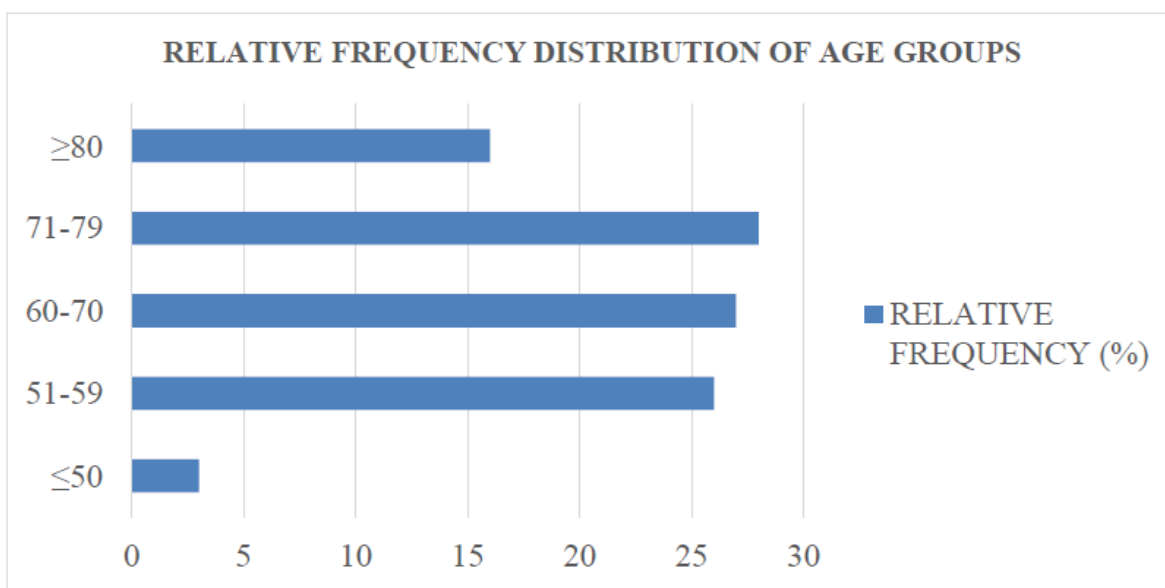


Figure 3.

Age groups distribution in exposed group is depicted in figure 4.

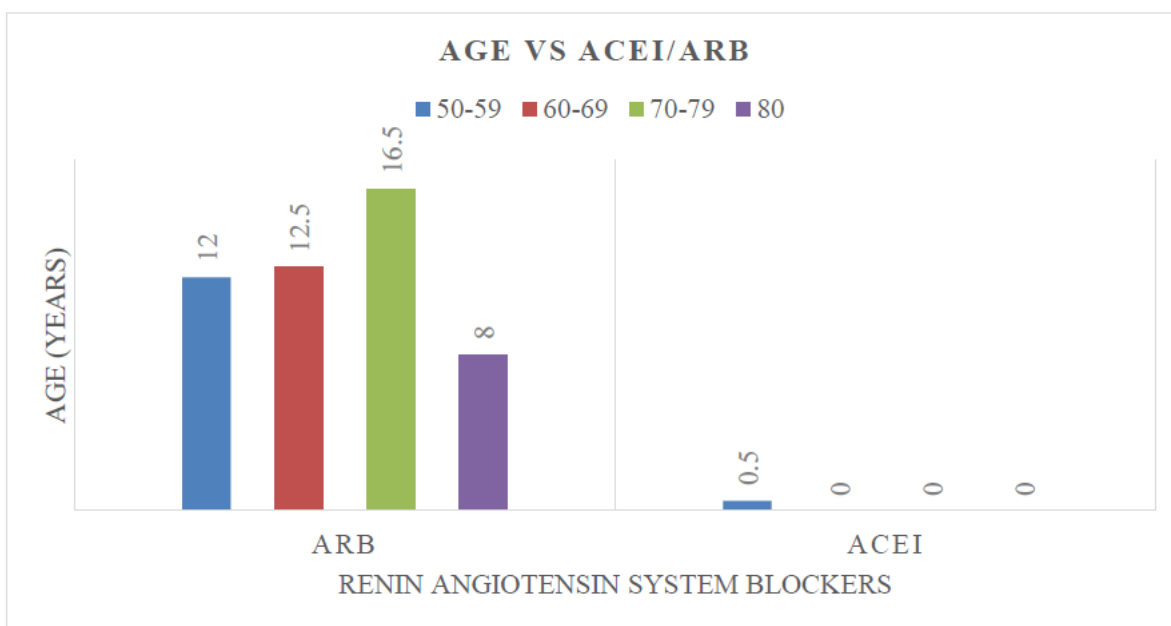


Figure 4

Figure 5 represents renin angiotensin receptor blockers and their average age distribution.

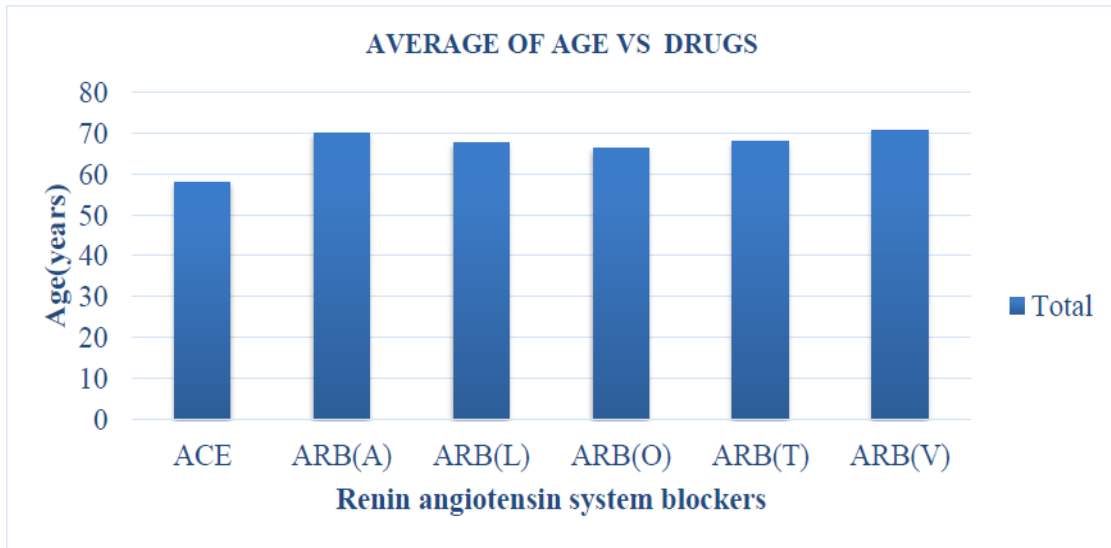


Figure 5

COMORBIDITIES

Table – 4

Comorbidities (N=200)	Non Exposed	Exposed	Total	Relative Frequency (%)
Ischemic Heart Disease	1	11	12	6 %
COVID 19	8	27	35	17.5 %
CAD	5	15	20	10%
CVA	5	7	12	6%
CHF	25	1	26	13%
Infections	0	21	21	10.5%

The table 4 demonstrates that from a total of 200 cases, the majority of the patients had COVID 19 (17.5%)

Figure 6 represents comorbidities in exposed group and in non-exposed group.

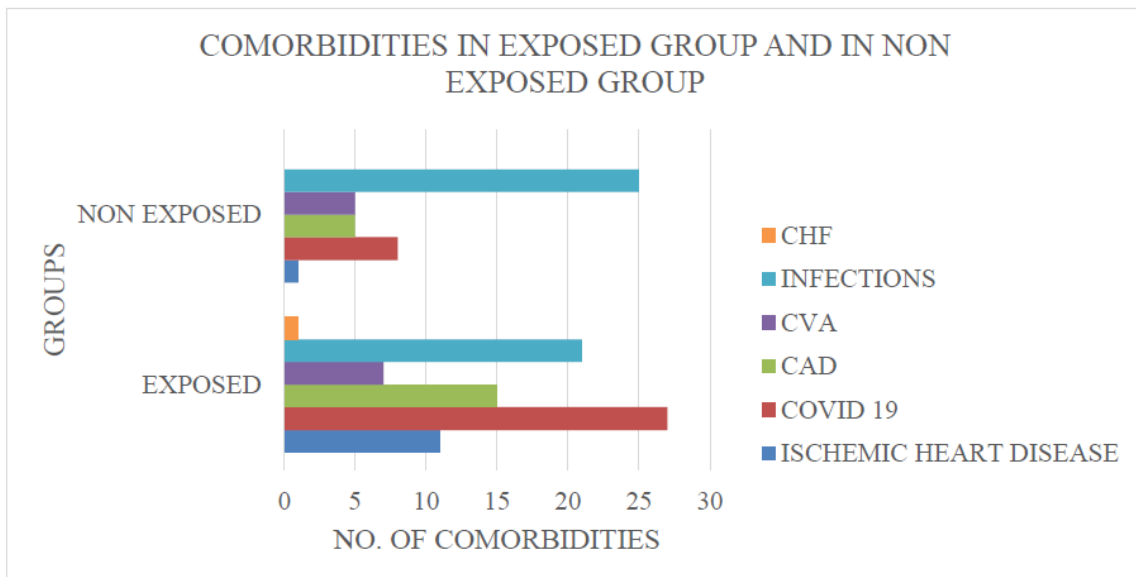


Figure 6.

BASELINE CHARACTERISTICS

Table -5.

PARAMETER (N=100)	VALUE (Mean ± Std.dev)
Average Serum Creatinine (mg/dL)	1.3±0.6
Average serum potassium (mEq/L)	4.1±0.5
Average baseline creatinine(mg/dL)	0.96 ±0.2
Systolic Blood Pressure (mmHg)	136.7±13.56
Diastolic Blood Pressure (mmHg)	81.6±7.74
BMI (kg/m ²)	24.6±2.3

Table -6.

PARAMETER (N=100)	VALUE (Mean ± Std.dev)
Average Serum Creatinine (mg/dL)	1.0±0.56
Average serum potassium(mEq/L)	3.9±0.36
Average baseline creatinine(mg/dL)	1±0.82
Systolic Blood Pressure (mmHg)	141.05±14.32
Diastolic Blood Pressure (mmHg)	82.5±8.35
BMI (kg/m ²)	24.1±3.37

Table 5 represents baseline characteristic of exposed group and table 6 represents baseline characteristics of non- exposed group which was consistent with prior reports in the literatures.^[6,7,8,9]

Table 7 shows that out of 100 cases, ACEIs were administrated to 1% of the patients (1/100) and ARBs to 99% (99/100) which was not consistent with prior reports in the literatures.^[6,7,8,9] This may be due to the increase potential to cause adverse events induced by ACEIs.

DISTRIBUTION OF RENIN ANGIOTENSIN SYSTEM BLOCKERS

Table – 7

Parameter (N=100)	Frequency And Relative Frequency
ARBs	99 (99%)
ACEIs	1 (1%)

Figure 7 represents the renin angiotensin system blocker users.

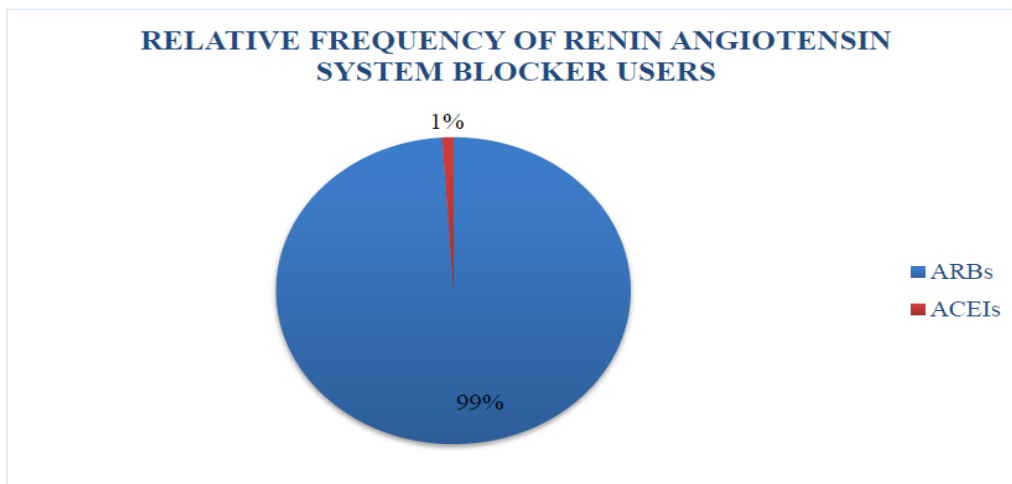


Figure 7.

BMI

Table – 8.

Bmi (n=100)	Frequency	Relative frequency (%)
<18	0	0
18-24.99	55	55
25-29.99	44	44
≥ 30	1	1
	100	100

Table 8 depicts Relative Frequency of BMI of Exposed group. The BMI of patients was $24.1 \pm 3.7 \text{ kg/m}^2$ in the non-exposed group and $24.6 \pm 2.3 \text{ kg/m}^2$ in the exposed

group which was consistent with prior reports in the literatures.^[6,7,8,9]

Figure 8 represents the relative frequency of BMI

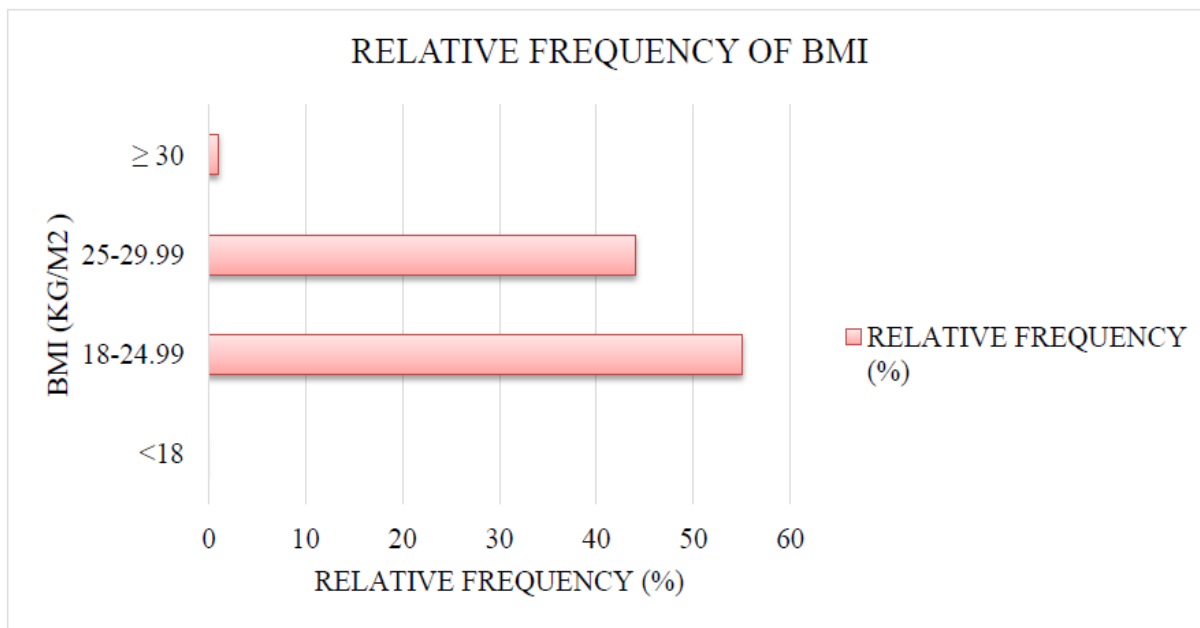


Figure 8.

SERUM CREATININE

The Average Serum Creatinine (mg/dL) in exposed group was found to be $1.3 \pm 0.6 \text{ mg/dL}$ and non-exposed group was found to be $1.0 \pm 0.56 \text{ mg/dL}$ which was similar to study of Mansfield KE et al.^[19]

represents the average of serum creatinine of renin angiotensin system blockers. The highest incidence percentage of increased creatinine according to the ARB type was associated with the use of telmisartan 10.7% (7/65 exposed), and olmesartan 14.2% (2/14 exposed), losartan 15.38% (2/13 exposed), which was similar to study of Mansfield KE et al.^[19]

Figure 9 represents the incidence of increased creatinine caused by renin angiotensin system blockers. Figure 10

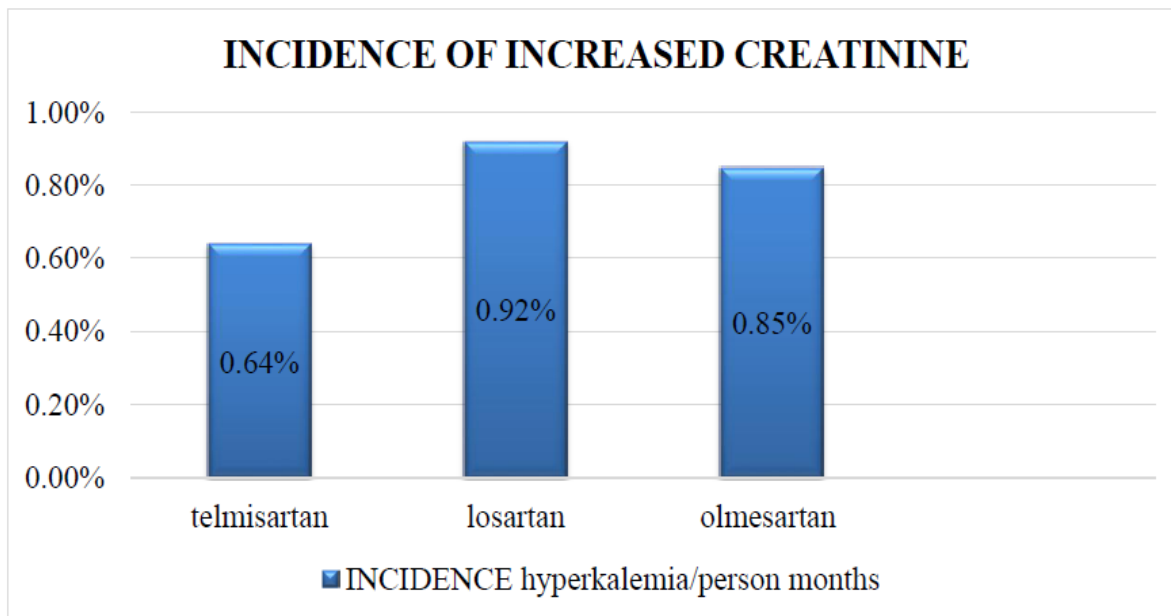


Figure 9.

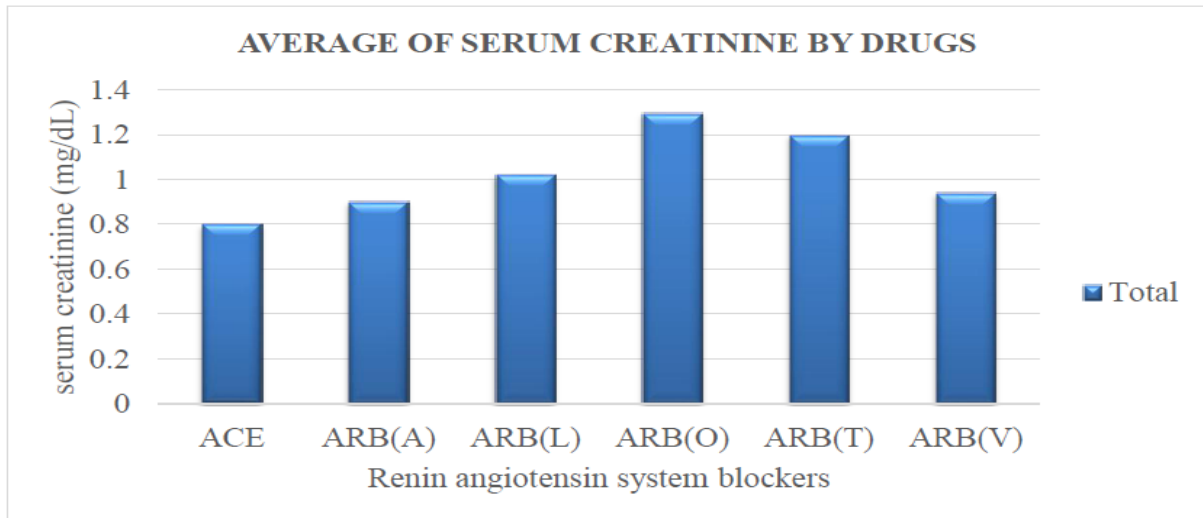


Figure 10

Figure 10 represents the average of serum creatinine of renin angiotensin system blockers.

ACE- Angiotensin converting enzyme inhibitor – Enalapril, ARB(A) – angiotensin receptor blocker

(Azilsartan), ARB(L) – angiotensin receptor blocker(Losartan), ARB(O) – angiotensin receptor blocker(olmesartan), ARB(T) – angiotensin receptor blocker (telmisartan), ARB(V) – angiotensin.

AKI STAGES

Table – 9

Aki Stages	Non exposed	Exposed	Total (n=200)	Relative Frequency (%)
Stage 0	98	89	187	93.5%
Stage 1	0	6	6	3%
Stage 2	2	3	5	2.5%
Stage 3	0	2	2	1%
	100	100	200	100%

The table 9 demonstrates that from a total of 200 cases majority had stage 1 (3.5%) followed by stage 2 (2.5%) and stage 3 (1%) AKI, which was consistent with prior study of Harzella A.^[20]

Figure 11 represents Stages of AKI and administration of ARBS/ACE –inhibitors.

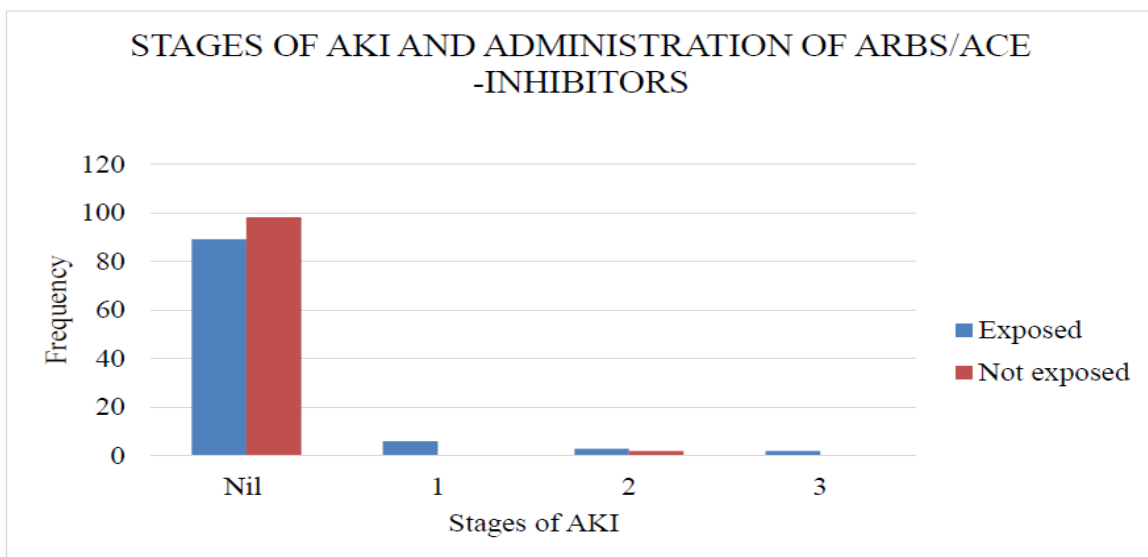


Figure 11.

ASSOCIATION OF STAGES OF AKI AND RENIN ANGIOTENSIN SYSTEM BLOCKERS

Table -11.

Stages of AKI (N=200)	FREQUENCY AND RELATIVE FREQUENCY		χ^2 test $\chi^2= 8.633,$ df= 3, p= 0.035* **Significant at 0.05 level
	Exposed (N=100)	Not-exposed (N=100)	
Nil	89 (44.5%)	98(49%)	
1	6(3%)	0(0%)	
2	3(1.5%)	2(1%)	
3	2(1%)	0(0%)	

From the table 11, it is shown that there was a significant association between stages of AKI and administration of ARBS/ACE -inhibitors ($\chi^2= 8.633, p<0.05$) which was similar to Mansfield KE, et al [19] with 95% CI and RR=1.12.

Figure 12 depicts the presence of AKI and administration of ARBS/ACE -inhibitors.

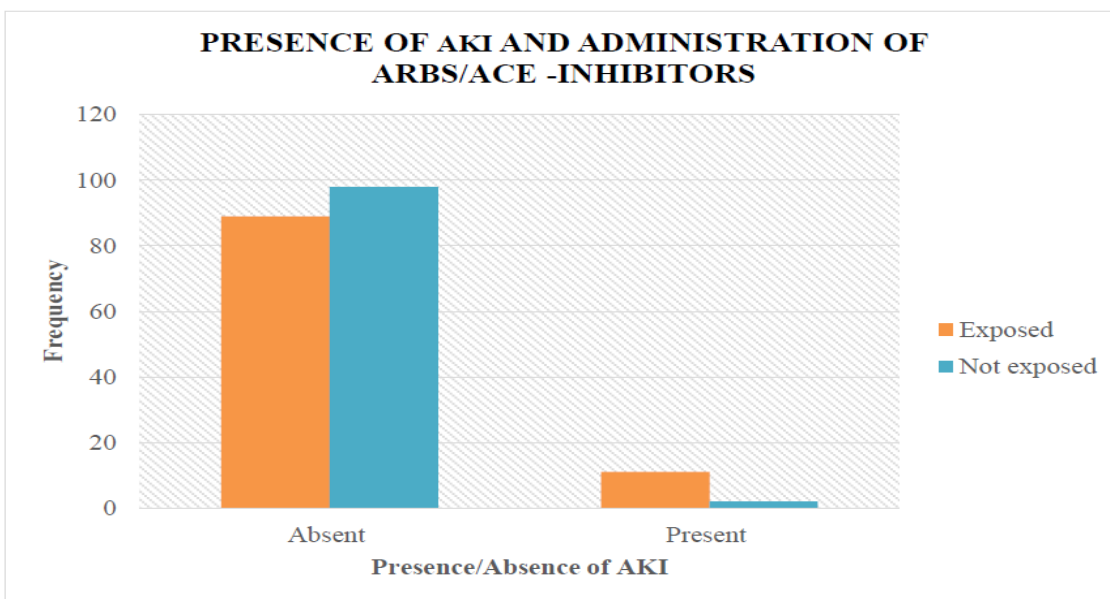


Figure 12.

RELATIVE RISK OF AKI BY RENIN ANGIOTENSIN SYSTEM BLOCKERS

Table -12.

AKI (N=200)	Group		Relative risk	χ^2 test $\chi^2= 6.664$ df= 1, p= 0.010** **Significant at 0.01 level
	Exposed (N=100)	Not-exposed (N=100)		
Absent	89(44.5%)	98(49%)	5.50	
Present	11(5.5%)	2(1%)		
Incidence rate	0.11	0.02		

Table 12 reveals the relative risk of AKI was significant among the sample exposed to ACEIs/ARBs in our study and was 5 times greater than the study conducted by Mansfield KE, et al. [6] with 95% CI and RR=1.12.

CORRELATION OF SERUM CREATININE WITH SERUM POTASSIUM

Table -13.

Variables	Mean	SD	r value	p value	Type of correlation
Creatinine level	1.17	0.65	0.618	<0.001***	Moderate positive
Potassium level	4.18	0.60			

Data presented in table 13 revealed that there was significant moderate positive correlation of creatinine level and Potassium level among samples exposed to ARBs/ACE inhibitors which was similar to study with prior reports in the literatures. [6,7,8,9]

Figure 24 depicts Scatter diagram representing moderate correlation of creatinine level and Potassium level among samples exposed to ARBS/ACE inhibitors.

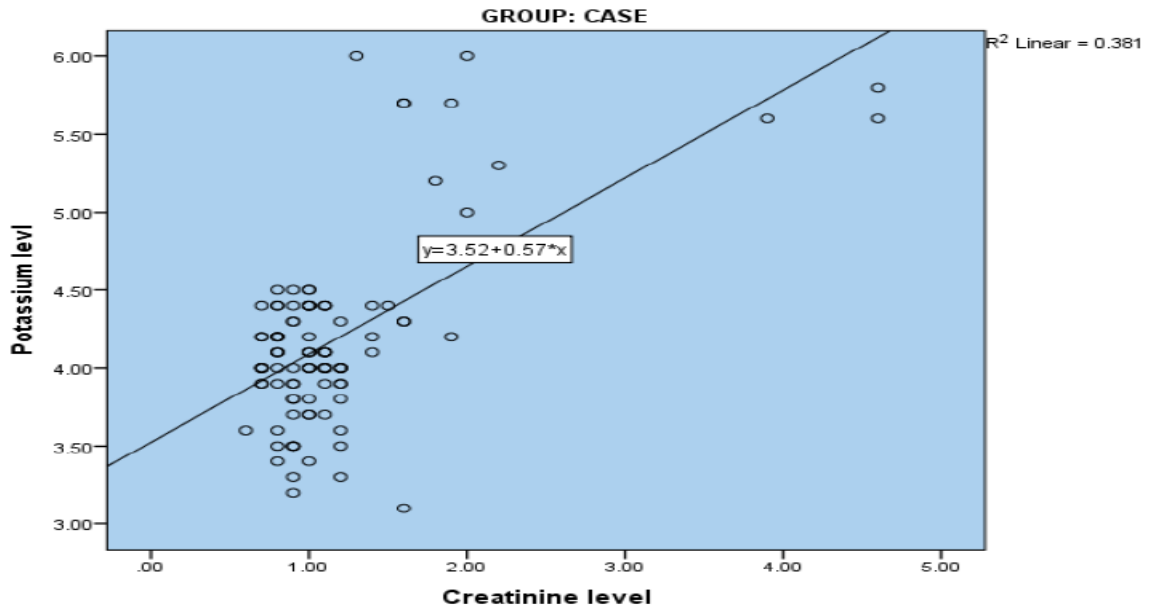


Figure 13.

Table 14.

Variables	Mean	SD	r value	p value	Type of correlation
Creatinine level	1.09	0.57	0.003	0.979 (NS)	Low positive
Potassium level	3.99	0.36			

Data presented in table 14 revealed that there was low positive correlation of creatinine level and Potassium level among samples not exposed to ARBs/ACE inhibitors which was similar to study with prior reports in the literatures.^[6,7,8,9]

Figure 14 depicts the Scatter diagram representing low positive correlation of creatinine level and Potassium level among samples not exposed to ARBs/ACE inhibitors.

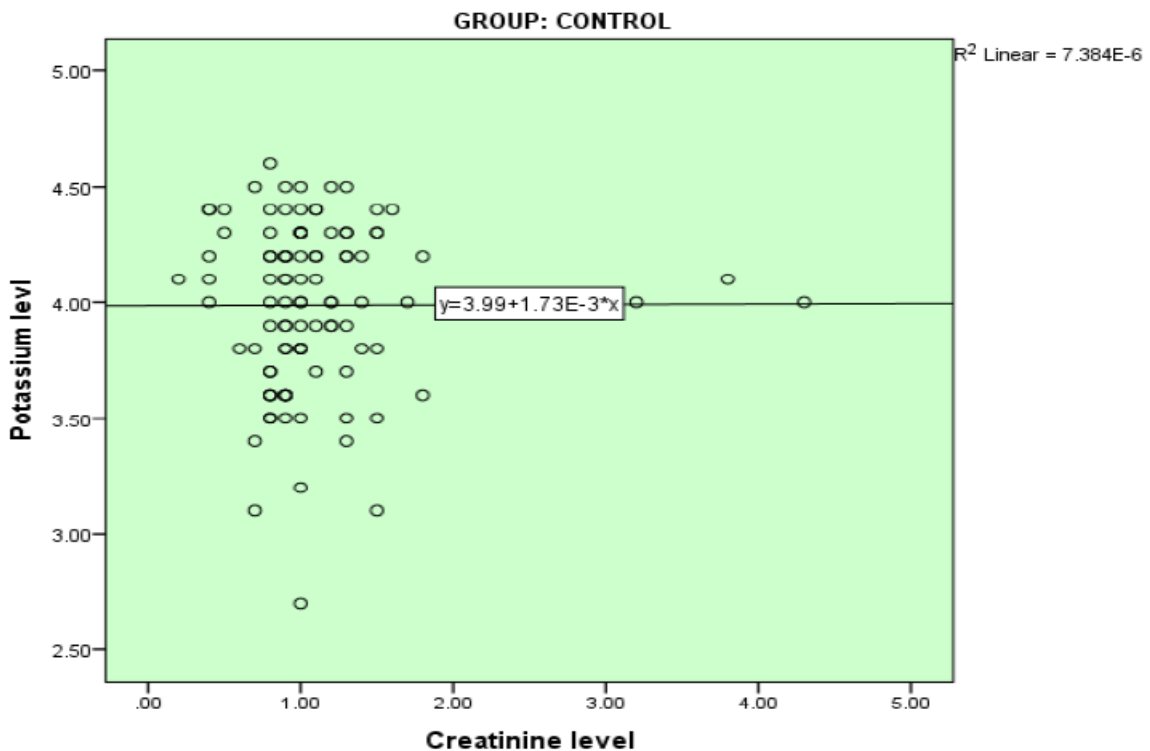


Figure 14.

CONCLUSION

A total of 100 patients' prescriptions were studied to evaluate if there was a risk of AKI associated with renin-angiotensin system blockers along with patient demographics, length of hospital stay. Our study helped to understand most commonly seen comorbidities and understand the risk of AKI and the adverse drug reaction associated and its severity in diabetes mellitus. A total of 11 (5.5%) patients with AKI were found associated with the use of renin-angiotensin system blockers. This study showed that the overall incidence rate of AKI in exposed to non-exposed group was 0.11 to 0.02 which explains that using Renin Angiotensin system blockers have significant association with AKI. The association of hyperkalemia induced by angiotensin receptor blockers were found to be statistically significant. On the other hand, there was no significant association with age, sex, duration of use, BMI, systolic and diastolic blood pressure. All of the adverse drug reactions were of mild severity and probably preventable respectively according to Hartwig's severity scale and preventability criteria assessed by modified Schumock and Thornton scale. ADRs are common occurrence but they are not often recognized. Even if they are recognized they are underreported as many are unaware about the clinical importance. The clinical pharmacist can provide their services by doing clinical interventions, inspecting patient care area and nursing station regarding use of renin angiotensin system blockers. Therefore, Implementation of multidisciplinary healthcare team including clinical pharmacist (Pharm D) will be beneficial to achieve the rational use of medicine, increase patient safety.

LIMITATIONS

- It was a retrospective study.
- This study was conducted in a short term duration, having small sample size and conducted in a single center.
- Only one patient was included in the study having ACEI as practitioners preferentially prescribe ARBs over ACEIs
- Patients are studied only while they are hospitalized. Therefore, any complications occurring after patients' discharge from their wards were not documented.
- Do not provide any information on the time frame of development of hyperkalemia

ACKNOWLEDGEMENTS

First and foremost, most humbly we thank God Almighty for the divine grace and blessings in making all these accomplishments made possible for me. It is our duty to render heartfelt thanks and gratitude to our most beloved Principal **Dr. Beena P** of KVM College of Pharmacy, and the authorities of SH Medical Centre, Kottayam for providing this opportunity to carry out this thesis work.

We would like to express our sincere gratitude to our respected thesis guide **Mr. Cijo George**, Associate Professor, Pharmacy Practice Department, KVM College of Pharmacy, for his sincere dedication and patience throughout this thesis, without his guidance this work wouldn't be completed.

We extend our special thanks to our co-guide **Miss Athira. S**, Assistant Professor, KVM College of Pharmacy for helping us in the successful completion of this thesis work. We extend our sincere gratitude to our class in-charge **Mr. Lijo Joseph Thomas** for all his guidance and support. We are very much thankful to **Mrs Chitra C Nair**, Head of the Department for their valuable support and help throughout the completion of our work. We owe a debt of heartfelt thanks to other group members for their support. We would like to express our love and gratitude to all our Pharmacy Practice Department Staff, for their support and encouragement. We would like to express our sincere thanks to all faculty and staff members of KVM College of Pharmacy for providing all necessary assistance and support.

We are grateful to our beloved parents and family members for their valuable feedback from time to time as well as their help and encouragement. We would also like to express my sincere gratitude to all our juniors.

We also wish to express our heartfelt gratitude to my dearest siblings for all their kind encouragements.

We wish to express our deep sense of gratitude to our dearest friends for providing us with a supportive and fun filled environment for the last five years. We are extremely thankful to all well-wishers who had contributed and contributing to our thesis.

With warm regards,
Miss.Akshitha D Ajay.
Miss Gini C Johns
Miss Mareena Mathew

REFERENCES

1. Bakris L G, Siomos M, Richardson D, Janssen I, Botton K W, Hebert L, et al. ACE Inhibition or angiotensin receptor blockade; Impact on potassium in renal failure. *Kidney International*, 2000; 58: 2084-2092.
2. Reardon C L, Macpherson S D. Hyperkalemia in outpatients using Angiotensin Converting Enzyme Inhibitors.How much should we worry? *Achieves of internal medicine*, 1998; 158(1): 26-32.
3. Schoolwetten C A, Sica A D, Ballermann J B, Wilcox S C. Renal Considerations in Angiotensin Converting Enzyme Inhibitor Therapy. *AHA journals*, 2001; 104: 1985-1991.
4. FitzSimmons SC, Agodoa L, Striker L, Conti F, Striker G. Kidney disease of diabetes mellitus: NIDDK initiatives for the comprehensive study of

- its natural history, pathogenesis, and prevention. *Am J Kidney Dis*, 1989; 13: 7-10.
5. Kostis JB, Shelton B, Gosselin G. Adverse effects of enalapril in the studies of left ventricular dysfunction (SOLVD). *Am Heart J*, 1996; 131: 350–355.
 6. Mansfield KE, Nitsch D, Smeeth L, et al. Prescription of renin– angiotensin system blockers and risk of acute kidney injury: a population-based cohort study. *BMJ Open*, 2016; 6: 1-9.
 7. Morten Schmidt ,Kathryn E Mansfield,Krishnan Bhaskaran, Dorothea Nitsch, Henrik Toft Sørensen, Liam Smeeth,Laurie A Tomlinson. Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study. *BMJ*, 2017; 356: 791.
 8. Bakris L G, SiomosM, Richardson D, Janssen I, Botton K W, Hebert L, et al.ACE Inhibition or angiotensin receptor blockade; Impact on potassium in renal failure.*Kidney International*, 2000; 58: 2084-2092
 9. Jun R H, Kim H, Lee H S, Cho H J, Lee H,Yim W H, et al. Onset of Hyperkalemia following the Administration of Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker. *Cardiovascular therapeutics*, 2021; 5935149.