THE IMPACT OF ANTIHYPERTENSIVE DRUG THERAPY IN PATIENTS WITH CHRONIC KIDNEY DISEASE: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

ALMAS SAFINA KAUSER1, HABEEB UNNISA1, AFIFA NAMREEN1, AYESHA SABA1, JAVED AKHTAR ANSARI*

1PharmD, Department of Pharmacy Practice, MESCO College of Pharmacy, Hyderabad, Telangana, India, *Professor, Department of Pharmacy Practice, MESCO College of Pharmacy, Hyderabad, Telangana, India

Email: javedAnsari47@gmail.com

Received: 12 Sep 2019, Revised and Accepted: 09 Nov 2019

INTRODUCTION

Chronic kidney disease (CKD) with its high prevalence, morbidity and mortality, is an important public health challenge [1]. According to the 2012 KDIGO clinical practice guidelines, CKD is defined as 'abnormalities of kidney structure or function, present for>3 mo, with implications for health'. Criteria for CKD (Either of the following presents for>3 mo): Markers of kidney damage (one or more): Albuminuria (ACR ≥ 30 mg/g), Urine sediment abnormalities, Electrolyte and other abnormalities due to tubular disorders, Pathological abnormalities detected by histology, Structural abnormalities detected by imaging, History of kidney transplantation; Decreased glomerular filtration rate (GFR)<60 ml/min/1.73 m² [2].

CKD and ESRD represent worldwide public health problems with an epidemic extent [3, 4]. From 1990-2013 the age-adjusted death rates attributable to CKD increased by 56.9% in 188 countries surveyed and CKD is now the 19th leading cause of life years lost [5]. In India, the incidence of CKD is rising and as per estimates from 2006, the age-adjusted incidence rate of ESRD is 229 per million population [6]. In 2015, CKD affected about 323 million people globally and resulted in 1.2 million deaths, up from 4,09,000 in 1990 [7]. The causes that contribute to the greatest number of deaths are hypertension at 2,38,000 [8].

Hypertension (HTN) is a major risk factor for cardiovascular and renal disease. Conversely, CKD is the most common form of secondary hypertension [9]. HTN is present in 50% to 80% of patients with CKD [10] defined as the persistent elevation of systolic blood pressure (SBP≥140 m Hg and diastolic blood pressure (DBP) ≥100 mmHg [11]. It is a strong independent, modifiable risk factor for CKD and contributes to the disease itself or, most commonly, to its progression [12]. It may develop early during the CKD and may contribute to adverse outcomes such as worsening of renal function or progression of kidney disease towards ESRD, development of cardiovascular diseases (CVD) such as heart attack and stroke and high cardiovascular morbidity and mortality [13-15].

Thus, HTN and CKD are inextricably linked with both cause and effect relationships [16]. It is well established that albuminuria and reduced GFR, in both diabetic and non-diabetic hypertensive CKD patients, are major cardiovascular risk factors and many older patients develop or die from cardiovascular disease rather than progress to ESRD [17, 18]. In particular, this may be due to inadequate control of HTN in patients with CKD [19].

There is some evidence that BP should be reduced below 130/85 mm Hg in patients with diabetic and non-diabetic nephropathies and<125/75 mm Hg in patients with non-diabetic nephropathies and proteinuria>1 g/day and the available data suggests that tight BP control (BP<140/90 mm Hg) can reduce the risk of cardiovascular complications in hypertensive patients with type 2 diabetes mellitus [20]. The JNC VIII guidelines for HTN in patients≥18 y old with CKD recommend a goal BP of<140/90 mmHg regardless of CKD stage or proteinuria. Other recommendations, including those by the KDIGO study in 2012, recommend a similar goal blood pressure of<140/90 mmHg in most CKD patients, but stricter control (<130/80 mmHg) in those with>30 mg/day proteinuria [21].

Aggressive treatment of HTN has been a key component [22] relevant at all stages of the disease, irrespective of the underlying cause [23, 25] as it is associated with improved cardiovascular outcomes in both CKD and ESRD [24]. Antihypertensive drugs are therefore recommended in patients with CKD with or without HTN as these agents provide cardio-protective and renoprotective...
benefits [25]. Antihypertensive drugs are therefore used in CKD to (1) Reduce BP; (2) Reduce the risk of CVD, and (3) slow the progression of kidney disease [26]. Recent guidelines for the treatment of HTN in CKD suggest the use of a variety of antihypertensive drugs to achieve the desired BP levels. Usually, a combination of two or more antihypertensive drugs is required to control HTN. Antihypertensive treatment is individualized to each patient depending on the age, severity of albuminuria, tolerance, compliance and specific clinical features [17, 21, 27].

In the present study, current evidence supporting treatment of HTN with antihypertensive drugs in CKD was reviewed and the study was therefore designed and performed to evaluate the impact of antihypertensive drug therapy in patients with CKD (Non-dialysis dependent) and ESRD (Dialysis dependent) in association with the patients' clinical or disease outcomes.

MATERIALS AND METHODS

The present study carried out to determine the impact of antihypertensive drug therapy in CKD patients with HTN. Ethical clearance was obtained from the Institutional Ethics Committee (No. MGP/IEC/ID/PD/PR/30) before the commencement of the project. The duration of the study was six (6) months. The study was carried out in the Inpatient Department of Nephrology, Osmania General Hospital, a tertiary care teaching hospital, Hyderabad, Telangana, India.

Study design

This is a hospital-based prospective observational cohort study. The patients were divided into two cohorts i.e.; non-dialysis dependent (NDD) and Dialysis dependent (DD) CKD based on the history of albuminuria, estimated glomerular filtration rate (eGFR) and the requirement for dialysis.

Study population

The study was conducted on 120 patients with presumed and/or confirmed CKD with HTN, but 18 patients were excluded based on the inclusion and exclusion criteria. 06 patients were lost to follow up, 12 patients were excluded after clinical judgment (AKI, Autoimmune disease, Current Infection, and Lactating woman; age<18). The remaining 102 patients were evaluated during the study.

Inclusion and exclusion criteria

After written informed consent was obtained following national guidelines, the subjects for the study were selected based on the following criteria that include: Patients of either sex, Age group ≥18years, Patients diagnosed as CKD Stages III-V and ESRD patients on hemodialysis. Terminally ill patients co-infected with HIV or hepatitis or with any infective conditions or with any autoimmune diseases, Patients of age group<18yrs, Patients with acute kidney injury (AKI), Surgical conditions like kidney stones, tumors, trauma and CKD patients with renal transplant, Pregnant and lactating women, individuals who are not willing to give consent were excluded.

Data collection

Proforma was designed covering all the necessary parameters. Data was collected from medical record sheet, patients and their attendants. The study related Physical examination, Clinical and Biochemical findings including BP (SBP and DBP), eGFR, serum electrolytes, serum creatinine, serum urea, albuminuria along with radiological findings including USG, X-ray and CT scan of the abdomen were documented and assessed at the time of admission and discharge as per the available literature. The data was used to determine the impact of antihypertensive drugs on the study cohorts.

Data analysis

The data was recorded, tabulated using Microsoft Excel 2007 version and descriptive analysis (mean, SD and range) performed using SPSS version 25.

RESULTS

A total of 102 patients were observed to study the cardio-protective and reno-protective effect of antihypertensive drugs during their stay at the hospital. These patients were divided into two cohorts viz. non-dialysis dependent (NDD) CKD (Cohort 1) and Dialysis dependent (DD) CKD (Cohort 2) depending upon the extent of kidney damage and dialysis required.
Table 1: Patients' characteristics in two cohort groups

| Characteristics                  | NDD-CKD (Cohort 1) N = 33 No. of Patients (%) | DD-CKD (Cohort 2) N = 69 No. of Patients (%) |
|----------------------------------|-----------------------------------------------|-----------------------------------------------|
|                                  | Male (n = 22)                                | Male (n = 37)                                |
| Age (years)                      | Female (n = 11)                              | Female (n = 32)                              |
|                                  |                                              |                                              |
| 18-27                            | 2 (1.96%)                                    | 3 (2.94%)                                    |
|                                  | 1 (0.98%)                                    | 2 (1.96%)                                    |
| 28-37                            | 5 (4.90%)                                    | 6 (5.88%)                                    |
|                                  | 1 (0.98%)                                    | 3 (2.94%)                                    |
| 38-47                            | 3 (2.94%)                                    | 11 (10.78%)                                  |
|                                  | 4 (3.92%)                                    | 5 (4.90%)                                    |
| 48-57                            | 1 (0.98%)                                    | 8 (7.84%)                                    |
|                                  | 1 (0.98%)                                    | 6 (5.88%)                                    |
| 58-67                            | 10 (9.80%)                                   | 7 (6.86%)                                    |
|                                  | 4 (3.92%)                                    | 11 (10.78%)                                  |
| ≥68                              | 1 (0.98%)                                    | 2 (1.96%)                                    |
|                                  | 0 (0.00%)                                    | 5 (4.90%)                                    |
| **Social History**               |                                              |                                              |
| Current Smoker                   | 3 (2.94%)                                    | 6 (5.88%)                                    |
|                                  | 0 (0.00%)                                    | 1 (0.98%)                                    |
| Ex-Smoker                        | 3 (2.94%)                                    | 2 (1.96%)                                    |
|                                  | 2 (1.96%)                                    | 0 (0.00%)                                    |
| Non smoker                       | 16 (15.69%)                                  | 29 (28.43%)                                  |
|                                  | 9 (8.82%)                                    | 31 (30.39%)                                  |
| **Co-morbidities**               |                                              |                                              |
| HTN (as cause)                   | 22 (21.57%)                                  | 33 (32.35%)                                  |
|                                  | 10 (9.80%)                                   | 4 (3.92%)                                    |
| Denovo HTN (as effect)           | 0 (0.00%)                                    | 4 (3.92%)                                    |
|                                  | 1 (0.98%)                                    | 0 (0.00%)                                    |
| Diabetes                         | 10 (9.80%)                                   | 8 (7.84%)                                    |
|                                  | 13 (12.75%)                                  | 12 (11.76%)                                  |
| CVD                              | 11 (10.78%)                                  | 16 (15.69%)                                  |
|                                  | 10 (9.80%)                                   | 28 (27.45%)                                  |
| Stroke                           | 0 (0.00%)                                    | 0 (0.00%)                                    |
|                                  | 1 (0.98%)                                    | 2 (1.96%)                                    |
| **Staging of CKD based on eGFR and Albuminuria** |                                               |                                              |
| G3a-A2                           | 0 (0.00%)                                    | 4 (3.92%)                                    |
| G3a-A3                           | 4 (3.92%)                                    | 1 (0.98%)                                    |
| G3b-A2                           | 1 (0.98%)                                    | 1 (0.98%)                                    |
| G3b-A3                           | 3 (2.94%)                                    | 0 (0.00%)                                    |
| G4-A2                            | 0 (0.00%)                                    | 0 (0.00%)                                    |
| G4-A3                            | 10 (9.80%)                                   | 3 (2.94%)                                    |
| G4-A3                            | 2 (1.96%)                                    | 1 (0.98%)                                    |
| G5-A3                            | 2 (1.96%)                                    | 0 (0.00%)                                    |
| G5-A3                            | 5 (7.84%)                                    | 27 (26.47%)                                  |

The mean age of CKD in NDD patients was 49.30±15.20 (Range=68-20) and in DD patients were 50.25±14.69 (Range=80-20). Majority of the patients (57.84%) were male in both the study cohorts (NDD=21.57% and DD=36.27%). In study cohorts, n=97(95.10%) were hypertensive (HTN as a CAUSE) and were receiving antihypertensive medications and n=5(04.90%) were newly diagnosed with HTN (HTN as an EFFECT). Most of the patients in both the cohorts were at G5/A3 stage (61.76%) followed by G4/A3 (15.69%).

Table 2: Percentage of antihypertensive drugs prescribed

| Antihypertensive drugs prescribed | Percentage (%) |
|-----------------------------------|----------------|
| RAS Antagonist                    | 26.47%         |
| Angiotensin                       |                |
| Converting Enzyme                |                |
| Inhibitors (ACEI)                 |                |
| Angiotensin II Receptor Blockers  | 2.94%          |
| (ARB)                             |                |
| Adrenergic Antagonists            | 2.94%          |
| Alpha Blockers (AB)               |                |
| Antagonists                       | 8.82%          |
| Beta Blockers (BB)                |                |
| Atenolol                          | 22.55%         |
| Metoprolol                        |                |
| Adrenergic Agonists               | 27.45%         |
| Centrally Acting Alpha2,.         |                |
| Agonist/Sympatholytic (CAAA/SYM)   |                |
| Calcium Channel                   | 21.94%         |
| Dihydropyridines (DHP)            |                |
| Blockers (CCB)                    | 7.84%          |
| Nifedipine                        |                |
| Cilnidipine                       | 1.96%          |
| Diuretics (D)                     | 2.94%          |
| Loop                              |                |
| Thiazide Like                     |                |
| Potassium Sparing                 |                |
| Spironolactone                    |                |

In both, the study cohorts, the most commonly prescribed class of antihypertensive drugs was diuretics (D) (93.40%) followed by calcium channel blockers (CCBs) (93.17%), Furosemide (84.30%) and Amlodipine (81.37%) were the most commonly prescribed antihypertensive drugs followed by Clonidine (27.45%) in combination with other antihypertensive drugs in the study cohorts. Antihypertensive drugs were prescribed alone or in combination based on the co-morbidities associated with CKD and HTN. All the patients (N=102) in the study were diagnosed with CKD and HTN with the evidence of albuminuria. Triple therapy (44.11%) was prescribed mostly in both the cohorts (NDD = 16.66%+DD = 27.45%).
Table 3: Percentage of antihypertensive drugs prescribed for the treatment of hypertension with associated co-morbidities in cohort 1 and cohort 2

| Hypertension and associated Co-morbidities | Antihypertensive therapy prescribed | Therapy received by NDD (%) | Therapy received by DD (%) |
|--------------------------------------------|------------------------------------|-----------------------------|---------------------------|
| CKD+HTN+Albuminuria (X = 102)              | CCB (DHP)                          | 0.98%                       | 4.90%                     |
| X+Fluid Overload                          | CCB (DHP)+D (loop)                 | 1.96%                       | 12.75%                    |
| Stage                                      | CCB+D (loop)+SYM                    | 0.00%                       | 1.96%                     |
| Pre                                         | AB+D (loop)+SYM                     | 0.00%                       | 0.98%                     |
| Normal (≤ 120/80)                          | CCB (DHP)+D (loop)+ABB              | 0.00%                       | 2.94%                     |
| Stage-1 Hypertension (140-159/90-99)       | CCB (DHP)+D (loop)+BB+SYM           | 0.00%                       | 3.92%                     |
| Cohort 1+2                               | CCB (DHP)+BB+SYM                   | 0.98%                       | 0.98%                     |
| X+DM                                      | CCB (DHP)+BB                        | 0.98%                       | 0.98%                     |
| X+CAD/PVD                                | CCB (DHP)+BB+SYM                   | 0.98%                       | 0.00%                     |
| X+Fluid overload+DM                       | CCB (DHP)+D (loop)+RAS              | 4.90%                       | 0.98%                     |
| Cohort 2                                  | BB+D (loop)+RAS+SYM                 | 0.00%                       | 0.98%                     |
| X+DM+CCF                                 | CCB (DHP)+D (loop)+RAS              | 0.98%                       | 0.00%                     |
| Cohort 2                                  | 3Ds (Loop, Potassium Sparing, Thiazide Like)+RAS+CCB | 0.00%                       | 0.98%                     |
| X+DM+CAD/PVD                             | CCB (DHP)+D (loop)+SYM              | 5.88%                       | 13.73%                    |
| X+Fluid overload+CCF                      | CCB (DHP)+D (loop)+RAS+SYM          | 0.98%                       | 0.00%                     |
| Cohort 2                                  | BB+D (loop)+RAS+SYM                 | 0.00%                       | 0.98%                     |
| X+DM+LVD/JVH+CAD/PVD                      | CCB (DHP)+D (loop)+RAS              | 0.98%                       | 0.00%                     |
| Cohort 2                                  | D (Potassium Sparing)               | 0.98%                       | 11.76%                    |
| X+DM+CAD/PVD                             | CCB (DHP)+D (loop)+RAS              | 0.98%                       | 2.94%                     |
| X+Fluid overload+DM+Stroke                | CCB (DHP)+D (loop)+BB               | 0.98%                       | 0.98%                     |
| Cohort 2                                  | CCB (DHP)+D (loop)+SYM              | 0.98%                       | 0.00%                     |
| X+DM+LVD/JVH+CAD/PVD                      | RAS+CB (DHP)+D (loop)+BB            | 1.96%                       | 0.00%                     |
| Cohort 2                                  | RAS+D (loop)+RAS                    | 0.00%                       | 0.98%                     |
| X+Fluid overload+DM+CAD/PVD+Stroke        | CCB (DHP)+D (loop)                  | 0.98%                       | 2.94%                     |

HTN = Hypertension, X = Hypertension+Albuminuria, DM = Diabetes Mellitus, LVD = Left Ventricular Dysfunction, LVH = Left Ventricular Hypertrophy, CAD = Coronary Artery Disease, PVD = Peripheral Vascular Disease, CCF = Congestive Cardiac Failure, HF = Heart Failure; AB = Alpha Blocker, ABB = Alpha + Beta Blocker, BB = Beta Blocker, CCB = Calcium Channel Blocker, DHP = Dihydropyridine, D = Diuretic, RAS = Renin Angiotensin System.

Table 4: Indication for antihypertensive drug therapy prescribed to the study cohorts

| Antihypertensive drug | Indication                                          |
|-----------------------|-----------------------------------------------------|
| AB (Prazosin), ABB (Labelatrolo), D (Metolazone) | Resistant Hypertension in DD patients |
| ACEI (Enalapril), ARB (Telmisartan)              | HTN, DM, Proteinuria and Decreased eGFR, CCF, CAD/PVD, CVA, |
| BB (Atenolol, Metoprolol)                         | HTN, DM to prevent CV complications, Angina, CCF, |
| CCBs (Amlodipine, Nifedipine, Cilnidipine)       | HTN, Angina, CVA                                  |
| D (Furosemide and Torsemide)                      | HTN, Fluid Overload, CCF, |
| SYM (Clonidine)                                    | HTN, Pulmonary oedema and LVH/VD                  |
| Potassium Sparing Diuretic (Spironolactone)        | HTN, Drug-Induced Hypokalaemia                     |

Table 5: Assessment of blood pressure during admission and discharge in cohort 1 and cohort 2 receiving antihypertensive therapy

| BP (mmHg) (SYSTOLIC/DIASTOLIC) | During admission No. of patients (Mean BP) | During discharge No. of patients (Mean BP) |
|--------------------------------|-------------------------------------------|-------------------------------------------|
|                               | NDD                                       | DD                                        |
| Normal (≤ 120/80)             | 1 (110)/0 (0)                             | 0 (0)/1 (70)                              | 2 (110)/3 (70) | 3 (110)/1 (60) |
| Pre-Hypertension (120-139/80-89) | 10 (130)/7 (80)                           | 10 (130)/8 (80)                           | 19 (127.4)/19 (80) | 46 (127.8)/35 (80) |
| Stage-1 Hypertension (140-159/90-99) | 9 (145.5)/14 (90)                      | 35 (147.1)/37 (90)                       | 9 (144.4)/10 (90)  | 20 (141.5)/33 (90) |
| Stage-2 Hypertension (≥ 160/100) | 13 (180)/12 (106.6)                     | 24 (176.7)/23 (104.5)                    | 3 (160)/1 (100)   | 0 (0)/0 (0)    |

n = No. of Patients.

In study cohorts, BP was calculated and assessed during hospital admission and discharge based on the JNC VIII 2014 guidelines for the staging of HTN. Cohort 1 and 2 at the Stage-1 HTN (during hospital admission) have found to be effectively responded to the antihypertensive therapy prescribed.

DISCUSSION

There is a strong association between CKD and an elevated BP whereby each can cause or aggravate the other. A higher BP is generally associated with a higher CVD risk, making BP lowering an attractive goal to reduce CV morbidity and mortality. Thus, BP control is fundamental to the care of patients with CKD and is relevant at all stages of CKD (NDD or DD) regardless of the underlying cause [23].

The predominance of the male in the study cohorts is similar to earlier studies [6, 17]. The prevalence of hypertension gradually increases as the predominance of the male in the study cohorts is similar to earlier underlying cause [23].

The predominance of the male in the study cohorts is similar to earlier underlying cause [23].
The study is limited by its sample size, unincisive nature, a short period of six months and few classes of drugs prescribed. Further follow-up of patients is needed to increase the understanding of long-term effects and outcomes.

CONCLUSION

In conclusion, the practice of prescribing antihypertensive drugs for the management of hypertension and to achieve blood pressure targets in chronic kidney disease (CKD) and end-stage renal disease (ESRD) remains uncertain. Although, the prescription of antihypertensive drugs has been based on the standard treatment guidelines (NKF KDOQI 2004 and KDIGO 2012), the development of new and revised guidelines suggesting novel and effective therapies is needed to reduce inappropriate variations in practice and promote better delivery of evidence-based treatment.

AUTHORS CONTRIBUTIONS

All authors contributed equally. All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Varughese S, Abraham G. Chronic kidney disease in India. Clin J Am Soc Nephrol 2018;13:3802-4.
2. Levin A, Stevens PE, Bilous RW, Goresh J, De Francisco ALM, de Long PE, et al. Kidney disease: improving global outcomes (KDIGO) CKD workgroup. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;83 Suppl 1:1–150.
3. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet: general information and national estimates on chronic kidney disease in the United States, 2010. Atlanta, GA: U. S. Department of Health and Human Services, CDC; 2010.
4. Eksioglu AS, Azab AE. Correlation between chronic kidney diseases and hematological data in sabratha hospital in Libya. Asian J Pharm Clin Res 2017;10:291-6.
5. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Textbook of pharmacotherapy— a pathophysiological approach. Chapter 44: Chronic kidney disease. 10th ed. New York: McGraw Hill; 2017. p. 1944–2015.
6. Singh AK, Farag YM, Mittal BV, Subramanian KK, Acharya VN, Keithiredy SR, et al. Epidemiology and risk factors of chronic kidney disease in India results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. BMC Nephrol 2013;14:114.
7. GBD 2015 Disease and Injury Incidence and Prevalence, Collaborators. (8 October 2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global burden of disease study. Lancet 2015;388:1545–602.
8. GBD 2015 Mortality and Causes of Death, Collaborators. (8 October 2016). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study. Lancet 2015;388:1459–544.
9. Teda FM, Brar A, Brownie R, Brown C. Hypertension in chronic kidney disease: navigating the evidence. Int J Hypertens 2011;2011:1-9.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. N Engl J Med 2004;351:1296–305.
11. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7). Hypertens 2003;42:1206-52.
12. Abraham G, Arun KN, Gopalakrishnan N, Renuka S, Pahari DK, Doshi P, et al. Management of hypertension in chronic kidney disease: consensus statement by an expert panel of Indian nephrologists. Asia Pac J Clin Nephrol 2017;65 Suppl 2:6-22.
13. Toto RD. Management of hypertensive chronic kidney disease: role of calcium channel blockers. J Clin Hypertens 2005;7(4, Suppl 1):15-20.
14. Ravera M, Re M, Deferrari L, Vettoretti S, Deferrari G. Importance of blood pressure control in chronic kidney disease. J Am Soc Nephrol 2006;17(4, Suppl 2):98-103.
15. Jacobsen P, Rossing K, Tarnow L, Rossing P, Mallet C, Pourier O, et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. Kidney Int 1999;56 Suppl 71:101-5.
16. Ritchie J, Rainone F, Green D, Alderson H, Chiu D, Middleton R, et al. Extreme elevations in blood pressure and all-cause mortality in a referred CKD population: results from the CRISIS study. Int J Hypertens 2013:1-8. http://dx.doi.org/10.1155/2013/597906.
17. Ptinopoulou AG, Pikilidou MI, Lasaridis AN. The effect of antihypertensive drugs on chronic kidney disease: a comprehensive review. Hypertens Res 2012;36:91-101.
18. ALLHAT Officers and coordinators for the ALLHAT collaborative research group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–97.
19. National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2, Suppl 1):1-266.
20. Salvetti A, Mattei P, Sudano I. Renal protection and antihypertensive drugs. Drugs 1999;57:665-93.
21. Gargiulo R, Suhail F, Lerva E. Hypertension and chronic kidney disease. Dis Mon 2015;6:1:387-95.
22. UK Renal Association eCKD guide; 2011. Available from: http://www.renal.org [Last accessed on 09 Jun 2019].
23. Becker GJ, Wheeler DC, De Zeeuw D, Fujita T, Furth SL, Haidas H, et al. Kidney disease: improving global outcomes (KDIGO) blood pressure workgroup. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:337-414.
24. Sinha AD, Agarwal R. Clinical pharmacology of antihypertensive therapy for the treatment of hypertension in CKD. Clin J Am Soc Nephrol 2018;14:757-64.
25. Kidney disease outcomes quality initiative (K/DOQI) clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004;43(5, Suppl 1):1-290.
26. Kidney disease outcomes quality initiative (K/DOQI) clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease: executive summary. Am J Kidney Dis 2004;43(5, Suppl 1):16-41.
27. Varma PV, Chakravarthi MR, Jyothsna G. Hypertension in patients with chronic kidney disease. Hypertens J 2016;2:28-34.
28. Parati G, Ochoa J, Bilo G, Agarwal R, Covic A, Dekker F, et al. Hypertension in chronic kidney disease part 1. Hypertens 2016;67:1093-101.
29. Jesky M, Lambert A, Burden AC, Cockwell P. The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population: a retrospective cohort study. Br Med J Open 2013;3:e003458.
30. Ku E, McCulloch C, Vittinghoff E, Lin F, Johansen K. Use of antihypertensive agents and association with risk of adverse outcomes in chronic kidney disease: focus on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. J Am Heart Assoc 2018;7:e009992.
31. Bakris G, Hart P, Ritz E. Beta-blockers in the management of chronic kidney disease. Kidney Int 2006;70:1905-13.
32. Calcium channel blockers and cardiovascular protection [Internet]. Escardio.org. 2019. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-6/Calcium-channel-blockers-and-cardiovascular-protection [Last accessed on 09 Jun 2019].