Research Article

Albumin creatinine ratio a predictor of coronary artery disease in essential hypertension patients

Manjula H S[1*], H V Shetty[2], Usha S M R[3], Priyadarshini K[4], Nandini M D[5], Victoria Ksh[6]

[1,5,6]Post Graduate II, [2]Professor and HOD, [3,4]Professor, Department of Biochemistry, RRMCH, Bangalore, Karnataka, INDIA.
Email: hsmanjula01@gmail.com

Abstract

Objectives: Hypertension is a global public health problem with one fourth adults worldwide estimated to have high blood pressure (BP). About 1 billion people are affected by hypertension worldwide and 7.1 million deaths per year may be due to hypertension. Hypertension is the commonest, asymptomatic, readily detectable, usually easily treatable chronic cardiovascular disorder of concern, posing major health problem to all socioeconomic strata due to its role in the causation of coronary heart disease, stroke and other vascular complications. Prevalence in the developing countries seems to be similar to that in the developed counties ranging from 10% to 20% among adults. In India, the prevalence of hypertension is 59.9 and 69.9 per 1000 males and females respectively in the urban and 35.5 and 35.9 per 1000 males and females respectively in rural populations. To reduce the burden of cardiovascular disease, management strategies are increasingly focusing on preventive measures following early detection of markers of atherosclerosis. Thus focuses on microalbuminuria which is gaining recognition as a simple marker of atherogenic milieu, one because it reflects sub clinical vascular damage in the kidneys and other vascular beds, it may also signify endothelial dysfunction that predispose to future cardiovascular events. **Methodology:** A total of fifty cases of hypertensive patients were taken for the study after satisfying the inclusion and exclusion criteria. Fifty age and sex matched normal individuals were included in the study under the control group. All patients were evaluated in detail and microalbinuria is defined as the albumin /creatinine ratio higher than 30mg/day and lower than 300mg/day. The spot morning urine sample was measured for microalbumin by Immunoturbidimetry method and for creatinine by Jaffe's method. **Results:** Mean albumin creatinine ratio were calculated and compared between cases and controls. The Albumin Creatinine Ratio mg/gm of creatinine in cases was (35.02±22.45) and in controls is (17.33±6.99) with p =< 0.001 which showed strong significance. Age distribution of patient studied showed positive correlation with borderline increase in ACR as age increased, mean ±SD in cases (56.82±11.69) and controls(50.62±10.81) p=0.007,significant Student T test. Stage II hypertensive with mean ±SD (42.86±24.87) and p value 0.003 showed positive correlation to ACR. Descriptive and inferential statistical analysis has been carried out in this study. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter group analysis) on metric parameters

Key Word: Albumin creatinine, coronary artery disease.

Address for Correspondence
Dr. Manjula H S, Post Graduate II, Department of Biochemistry, RRMCH, Bangalore, Karnataka, INDIA.
Email: hsmanjula01@gmail.com
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INTRODUCTION

Hypertension is a global public health problem with one fourth adults worldwide estimated to have high blood pressure (BP)[1]. About 1 billion people are affected by hypertension worldwide and 7.1 million deaths per year may be due to hypertension. Hypertension is the commonest, asymptomatic, readily detectable, usually easily treatable chronic cardiovascular disorder of concern, posing major health problem to all socioeconomic strata due to its role in the causation of coronary heart disease, stroke and other vascular complications. Prevalence in the developing countries

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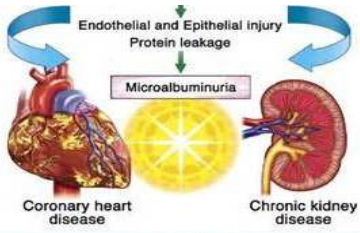
seems to be similar to that in the developed counties ranging from 10% to 20% among adults. In India, the prevalence of hypertension is 59.9 and 69.9 per 1000 males and females respectively in the urban and 35.5 and 35.9 per 1000 males and females respectively in rural populations.[2,3] CVD deaths due to Hypertension as a major risk factor is 2.7 million in 2004. It is expected to cross 4 million by 2030. (WHO published in March 16th 2013) Essential Hypertension tends to be familial and likely to be the consequence of an interaction between environmental and genetic factors .[5]The incidence of hypertension continues to increase in all developed and developing societies as the population grows older and more obese.[2]The Framingham Heart study and other epidemiological surveys have clearly defined hypertension as an important cause of morbidity and mortality.[1, 6, 7]

According to WHO report 2003, cardiovascular disease was responsible for 16.7 millions of total global death and 3.9 millions only from hypertension.[1] To prevent various complications hypertension demands proper diagnosed and adequate treatment. Hypertension is considered the most common and importance cardiovascular morbidity in general adult population.[8] Coronary artery disease is a major cause of death and disability in both developed and in developing countries. CAD is multifactorial disorder with several different risk factors. Advancing age, male sex, hypertension, diabetes mellitus, cigarette smoking and dyslipidemia are the major and independent risk factors for CAD. Many individual new biomarkers have been related to cardiovascular risk including levels of CRP(C reactive protein), B –type natriureticpeptide (BNP), fibrinogen, D-Dimer and homocysteine. Among these new biomarkers is microalbuminuria, which is gaining recognition as a marker of an atherogenesis owing to its association with several atherosclerotic risk factors and early systemic vascular (endothelial) damage .Aim of this study was to assess the albumin creatinine ratio as a new predictor for CAD and to correlate with severity apart from other traditional CAD risk factor[9].

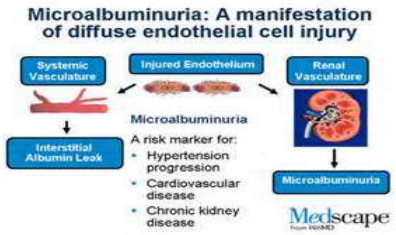


The definition of MA has been refined; the current National Kidney Foundation definition of MA is a urinary excretion rate of albumin between 20µg/min and 200µg/min or between 30mg/d and 299mg/d .Although 24-hour collections were the traditional way to measure MA, a quick and comparably accurate way of measuring albuminuria was an albumin/creatinine ratio on a spot collection of morning urine in the fasting state. With the growing use of the spot urine collection approach, the definition of MA was expanded to include a urinary albumin/creatinine ratio(UACR) of 2 to 20 mg albumin/mmol creatinine(30-299mg/g);the use of this ratio depends on factors like albumin excretion-blood pressure ,salt intake, time of the day, volume status creatinine excretion – gender, race, muscle[10].

Microalbuminuria is defined as UACR> 3.5mg/mmol (female) or> 2.5 mg/mmol (male) or with both substances measured by mass as a UACR between 30 and 300µg albumin /mg creatinine. An alternative definition of microalbuminuria is a UACR on a random urine sample of more than 30mg (but less than 300mg) of a albumin per gram of creatinine (2-3).[11]

Urinary albumin levels can vary widely from sample to sample in the same patient, with day-to-day intraindividual coeficients of variation as high as 50%.Factors that increase urinary albumin excretion includes urinary tract infection, congestive heart failure, exercise, fever, poor glycemic control, and vaginal discharge. By obtaining a first morning sample we can minimize the effect of exercise. A first morning void sample is considered best because it has a lower within – person variation for the albumin: creatinine ratio than a random urine sample. In view of all these considerations, the American Diabetes Association and the National Kidney Foundation demand at least two elevated albumin-to-creatinine ratios separated by 3 or 6 months to make the diagnosis of microalbuminuria.[12] There are several laboratory methods for measuring urinary albumin exception like, Radioimmunoassay, ELISA, and Immunoturbidimetry. All of them appear to have similar sensitivity and specificity. The pathophysiological mechanisms involved in MA are local injury to the vascular smooth muscle and endothelial cells through vessel shear stress, and subsequent changes in nitric oxide and increases in a variety of cytokines that culminate in cell proliferation and increases in vascular permeability.

The mechanism explaining the association between microalbuminuria and cardiovascular disease remains unknown. Microalbuminuria in non-diabetic individuals seems to be a sign from the kidney that the vasculature, mainly the endothelium, is not functioning properly. This fact may be confirmed by the following evidencences. Vasodilatation in response to some stimuli is reduced in normal elderly individuals with microalbuminuria values compared with those without albuminuria. Among non-diabetic hypertensive individuals, these with microalbuminuria show higher levels of von-willibrand factor than those without microalbuminuria. Some von willibrand factor has been associated with occlusive thrombosis, elevations of this factor may contribute to an increase in cardiovascular disease.[13] Microalbuminuria could also be considered a marker of inflammation in multiple inflammatory processes such as sepsis, trauma, acute pancreatitis, and acute respiratory distress syndrome.



Albumin excretion in random urine sample is expressed as a ratio to the creatinine concentration. As its excretion is constant during day as long as GFR remains constant. Never varies with concentration of urine. Not affected by diet, age and exercise.

OBJECTIVES OF THE STUDY

To estimate urine albumin by Immunoturbidimetry method. To estimate urine creatinine by Jaffe's method. To estimate urine albumin creatinine ratio. To estimate serum creatinine in blood sample to rule out renal pathology.ECG was done to rule out cardiovascular disease.

METHODOLOGY

INCLUSION CRITERIA

Fifty essential Hypertension patients attending general medicine OPD, Rajarajeswari Medical College and Hospital, Bangalore. Including prehypertension and patients on medication with ACE and ARB Inhibitors. Criteria for cases were diagnosed essential hypertensive patients with SBP >140mmHg and DBP > 90mmHg of either sex between age group 25-75 yrs. Fifty age matched healthy subjects without essential hypertension were included in the control group. Ethical clearance was obtained from the ethical clearance committee of RRMCH, Bangalore. There were no financial liabilities on the study subjects.

EXCLUSION CRITERIA

Patients with secondary hypertension and complications of Cardiovascular, renal disorders and stroke. History of multiple transfusions, renal disease. Pregnancy, anemia and history of any other medical or surgical illness.

CONTROL GROUP

Normal volunteers in the age group of 25-75years will be screened for same parameters which are done for cases.

METHOD OF COLLECTION OF DATA

Blood sample from the study and control group were drawn under full aseptic precautions, after obtaining informed consent. Early morning first spot urine sample is collected for Albumin and Creatinine estimation. Fasting blood sample will be collected in Clot Activator and fluoride EDTA vacuum evacuated tubes from both study and control group under full aseptic precautions after obtaining informed consent. The biochemical parameters are estimated using the following methods: Creatinine is estimated by Jaffe's method. Albumin is estimated by Immunoturbidimetric method. In Serum creatinine was estimated by Jaffe's method.

STUDY DESIGN: An observational case-control correlation study.

RESULTS

Table 1: Age distribution of patients studied

Age in years	Cases		Controls	
	No	%	No	%
31-40	4	8.0	10	20.0
41-50	14	28.0	17	34.0
51-60	13	26.0	12	24.0
61-70	11	22.0	9	18.0
>70	8	16.0	2	4.0
Total	**50**	**100.0**	**50**	**100.0**
Mean ± SD	**56.82±11.69**		**50.62±10.81**	

P=0.007**, Significant, Student t test

Mean urine albumin creatinine ratio was more among cases compared to controls which was found to be statistically significant χ^2 = (P=0.007)

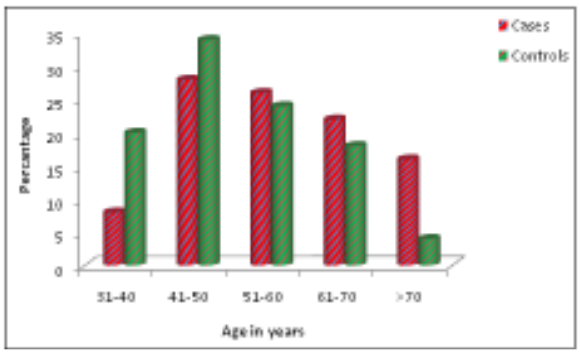


Table 2: Gender distribution of patients studied

Gender	Cases		Controls	
	No	%	No	%
Female	24	48.0	19	38.0
Male	26	52.0	31	62.0
Total	50	100.0	50	100.0

P=0.313, Not significant, Chi-Square test

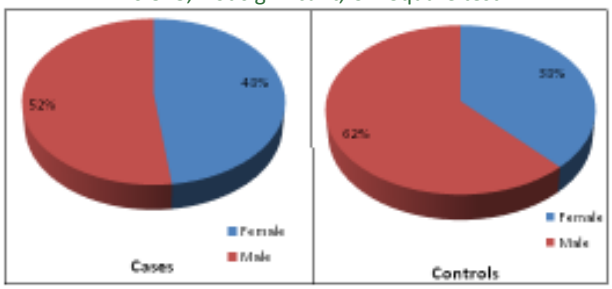


Table 3: Stage of Hypertension

Stage of Hypertension	No. of patients	%
I	21	42.0
II	29	58.0
Total	**50**	**100.0**

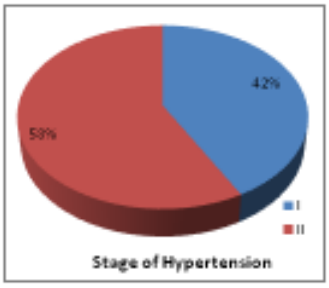


Table 4: Albumin creatinine Ratio mg/gm of C

Albumin creatinine Ratio mg/gm of C	Cases		Controls	
	No	%	No	%
<10.7	4	8.0	11	22.0
10.7-20	14	28.0	22	44.0
>20	32	64.0	17	34.0
Total	50	100.0	50	100.0

P=0.008**, Significant , Chi-Square test

Albumin creatinine ratio among cases showed significant rise with p = 0.008 when compared with controls.

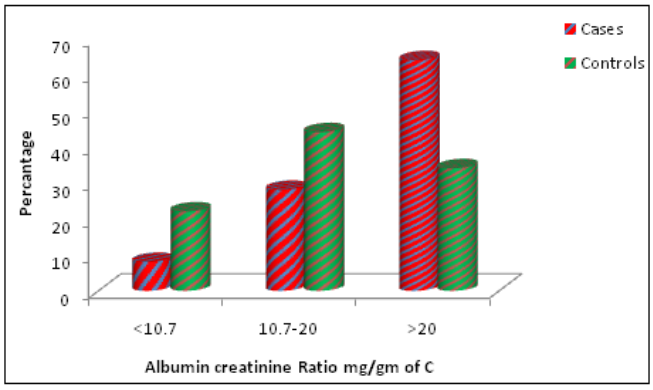


Table 5: Comparison of variables in case and controls

	Cases	Controls	P value
Albumin creatinine Ratio mg/gm of C	35.02±22.45	17.33±6.99	<0.001**
Sodium	139.10±4.15	137.50±3.01	0.036*
Potassium	4.00±0.47	3.80±0.23	0.008**
Urea	29.29±6.01	25.94±5.50	0.006**
Serum Creatinine	1.02±0.18	0.97±0.15	0.100

Serum electrolytes, blood urea, serum creatinine was estimated in both cases and controls to rule out renal pathology. Creatinine showed no significant rise in both cases and controls

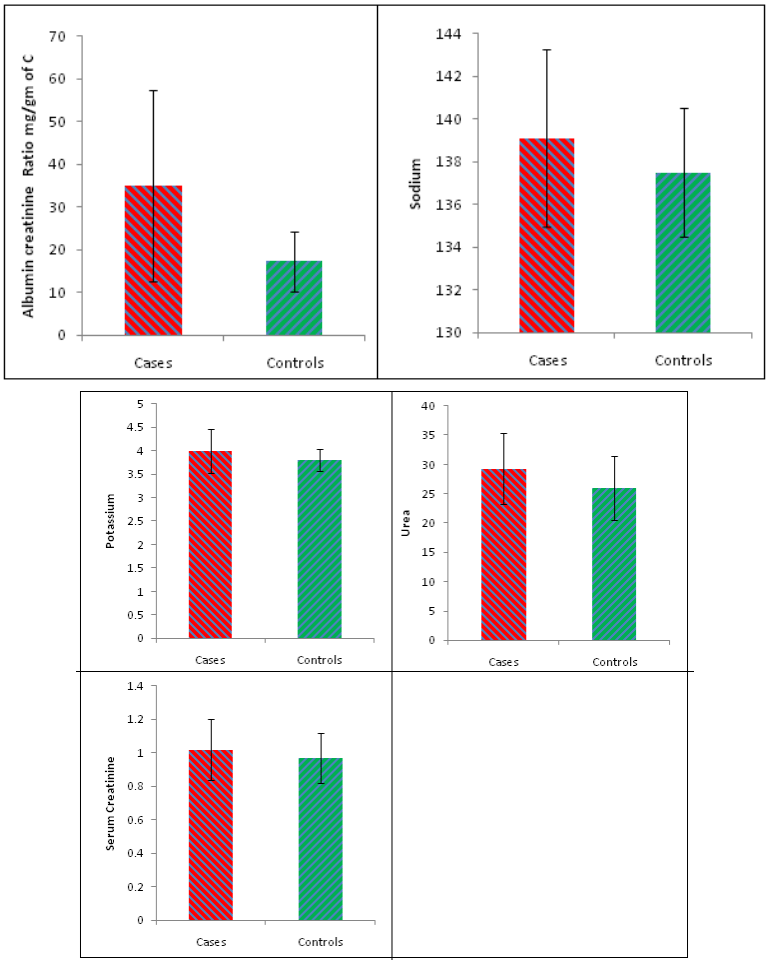
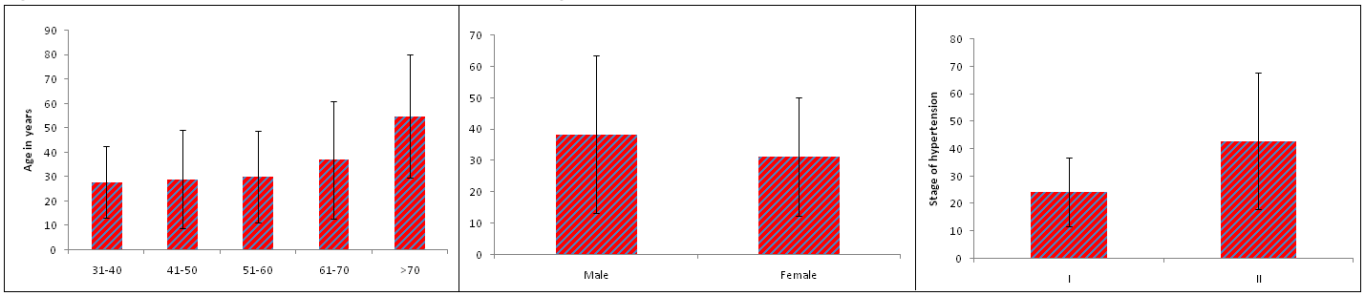


Table 6: levels of Albumin creatinine Ratio mg/gm of C according to age, gender and stage of hypertension

Albumin creatinine Ratio mg/gm of C	Min-Max	Mean ± SD	95% CI	P value
Age in years				
• 31-40	7.93-43.00	27.83±14.69	4.463-51.202	
• 41-50	7.70-73.00	28.98±20.13	17.357-40.600	
• 51-60	7.60-63.50	29.96±18.89	18.541-41.375	0.073+
• 61-70	10.96-73.50	36.96±24.13	20.750-53.170	
• >70	23.40-81.30	54.74±25.27	33.610-75.865	
Gender				
• Male	7.60-81.30	38.39±25.22	28.200-48.572	0.274
• Female	7.93-73.50	31.37±18.86	23.408-39.332	
Stage of Hypertension				
• I	7.70-47.00	24.19±12.51	18.494-29.881	0.003**
• II	7.60-81.30	42.86±24.87	33.403-52.322	

As the age increases the Albumin creatinine ratio is increasing significantly with p=0.073, there is no difference with gender and Albumin creatinine ratio is significantly more with Stage II Hypertension.
Age with Albumin creatinine ratio is borderline significant.



STATISTICAL METHODS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions: 1.** Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, Cases of the samples should be independent. Student "t" test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. 95% Confidence Interval has been computed to find the significant features. Confidence Interval with lower limit more than 50% is associated with statistical significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value:0.01<P ≤ 0.05)
** Strongly significant (P value: P≤0.01)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

DISUSSION

Mean albumin creatinine ratio were calculated and compared between cases and controls. The Albumin Creatinine Ratio mg/gm of creatinine in cases was (35.02±22.45) and in controls is (17.33±6.99) with p =< 0.01 which showed strong significance. Age distribution of patient studied showed positive correlation with borderline increase in ACR as age increased, mean ±SD in cases (56.82±11.69) and controls(50.62±10.81) p=0.007,significant Student T test. Stage II hypertensive with mean ±SD (42.86±24.87) and p value 0.003 showed positive correlation to ACR. Descriptive and inferential statistical analysis has been carried out in this study. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (inter group analysis) on metric parameters. The study results showed the strong association of albumin creatinine ratio among essential hypertensive patients. There was increase in ACR in patients with stage II hypertension and there was increase micoalbuminuria with increase in age. In this study cases included 58% of male patients and 42% female patients but there was no difference in ACR with gender. Electrocardiogram was done which showed left

ventricular hypertrophy in many patients, which shows the risk of cardiovascular disease. Hypertension is considered the most common and the importance cardiovascular morbidity in general adult population. Many recent studies demonstrated that microalbuminuria is also associated with worse cardiovascular outcomes in hypertension and in general population. Parving *et al*, in 1974 was the first to report microalbuminria in hypertensive patients without diabetes. Since then several studies have shown the true prevalence of microalbuminuria in essesntial hypertension varies in the range 20-40%, according to the selection criteria used.[1] According to Jan Skov Jensen *et al*, microalbuminuria confers a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects. Urinary albumin excretion should be measured regularly in hypertension clinic and a rigorous control of blood pressure and of other atherosclerotic risk factors is recommended in hypertensive patients with microalbuminuria.[14] Ricardo *et al* showed the prevalence of microalbuminuria in hypertensive individuals in high and is even higher in patients with coronary artery disease .There is a correlation between the presence of microalbuminuria and age, diabetes, and dyslipidemias. Microalbuminuria is a strong predictor of the occurrence of coronary artery disease.[13] The HOPE study showed that the presence of microalbuminuria was associated with the increased relative risk of primary end points (myocardial infarction, stroke or cardiovascular death). The LIFE study on hypertensive patients with ECG evidence LVH showed that for every increase of 10 times in albumin creatinine ratio, the risk of infarction or stroke increased by 57% and the risk of cardiovascular death 98% the non diabetic patients. Increases in diabetic patients were of 39% and 47% respectively. Bibek poudal *et al* found strong association between microalbuminuria and hypertension. Hypertension is the established risk factor for cardiovascular disease and renal disease. By showing strong association between MAU and hypertension. Our findings suggest that MAU could be a useful marker to assess risk management of cardiovascular disease and renal disease[15]

Kristian wachtell *et al* showed increased UACR results in increasing risk for cardiovascular morbidity and mortality among hypertensive patients with left ventricular hypertrophy.[16]

CONCLUSION

Hypertension is the established risk factor for cardiovascular disease and renal disease. These hypertensive patients have to be periodically monitored to keep watch for any cardiovascular risk or changes. MA estimation is one such marker for the assessment of cardiovascular disease risk in hypertensive patients. ACR is economical and simple biochemical marker which can be used to monitor the hypertensive patients who are prone to develop cardiovascular disease or renal disease. The present study has defined the temporal relationship between blood pressure and microalbuminuria in essential hypertension. We can conclude that the more effective the BP controls, the lower the risk of developing microalbinuria. Consequently, the maintenance high BP may have a key pathogenic role in the development of MAU.

Moreover, defining the risk of MAU at an early stage would be ideal for guiding therapies geared to the prevention of progression. This prompt intervention to avoid the development of MAU may result in better protection against hypertension –induced organ damage.

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