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ABSTRACT

Objective: The objective of this study was to compare renal function in diabetic hypertensive chronic kidney disease patients receiving enalapril or losartan.

Design: This was a retrospective analytic cohort study.

Setting: Kenyatta National Hospital, Nairobi, Kenya.

Subjects: Two hundred adult patients with hypertension and diabetic nephropathy.

Interventions: One hundred and sixteen participants received an enalapril regimen while 84 were on a losartan regimen.

Main outcome measures: time to doubling of serum creatinine and changes in the levels of proteinuria.

Results: There was a higher risk of doubling of serum creatinine with losartan (Adjusted HR=1.572; [95% CI:1.015-2.434]; p=0.043) than enalapril. There was a significant difference in time to doubling between the two arms – losartan 18 months, enalapril 36 month (p=0.046). The changes in the levels of proteinuria between the two arms were not statistically significant for most of the follow up period except at the 15th month from treatment initiation (p=0.05).

Conclusions: Enalapril was found to be more reno-protective compared to losartan. Where feasible, we suggest local use of enalapril as opposed to losartan for diabetic hypertensive chronic kidney disease patients.

INTRODUCTION

Chronic kidney disease (CKD) is an increasing health concern associated with adverse outcomes. Its prevalence is increasing at a rate of 8% per year worldwide (1). The etiology of CKD differs by region, age, gender and race. In Europe, Japan and the United States, diabetic nephropathy is the leading cause of CKD, while in the developing world, chronic glomerulonephritis and systemic hypertension are the leading causes (1).

Renin Angiotensin Aldosterone System (RAAS) modifiers such as Angiotensin Converting Enzyme (ACE) inhibitors and the Angiotensin Receptor Blockers (ARBs) are used to control blood pressure and also to retard the progression to end stage renal failure (2). Enalapril (an ACE inhibitor) and losartan

(an ARB) are commonly used at the renal and diabetic clinics in Kenyatta National Hospital (KNH), the largest teaching and referring hospital in Kenya.

Reliable statistics for End Stage Renal Disease (ESRD) are lacking in African countries. It is however noted that CKD is at least three to four times more prevalent in Sub Saharan Africa than in more developed countries (3). In East and Central Africa, it is reported that there is poor response to treatment and faster progression to renal failure.

ACE inhibitors are useful in treating diabetic nephropathy since they reduce proteinuria and stabilize renal function which may be independent of blood pressure lowering. This benefit may be due to improved renal hemodynamics with decreased glomerular efferent arteriolar resistance and a drop in the intra-glomerular capillary pressure (4).

ARBs block the angiotensin type 1 receptor (AT₁). The incidence of cough with these drugs is very low compared to ACE inhibitors. They are also considered to offer a more complete inhibition of angiotensin action (4).

More recently, direct renin inhibitors have been in use (Aliskerin®) and they block the RAAS at its point of activation, resulting in reduced plasma renin activity and blood pressure lowering (5). There is not much long term data available on this class of drugs. Clinical trials are still ongoing to evaluate their usefulness (6).

Local studies have evaluated the adequacy of blood pressure control in patients with CKD and hypertension (7, 8). However, these studies neither investigated nor compared renal function in patients who were on either ACE inhibitors or ARBs. There is therefore a paucity of local data regarding the use of these drugs and the renal outcomes. Most studies comparing renal outcomes in patients using these drugs have been done in Europe, Asia and the United States with the inclusion of few black patients. Furthermore, there may be differences in how local populations respond to therapy to treatment by ACE inhibitors and ARBs compared to populations in Western and Asian countries.

The aim of this study was to compare the effects of losartan and enalapril therapies on renal function in diabetic patients with hypertension. The time to and incidence of doubling of baseline serum creatinine levels as well as changes in levels of proteinuria were compared.

MATERIALS AND METHODS

Ethical approval was granted by the Kenyatta National Hospital Ethics and Research Committee (KNH-ERC/A/140) to carry out a retrospective analytic cohort study at the hospital's renal and diabetic clinics. Patient files dating back seven years (January 2006-December 2012) were perused. Good Clinical Practice (GCP) guidelines were adhered to as outlined by the International Conference on Harmonization (ICH). Confidentiality of the patients' medical records was maintained and no names were included during data collection. Patients were assigned study numbers in place of hospital patient identification numbers. A link log was created and kept under lock and key accessible only by the principal investigator. All original records pertaining to the study were also kept under lock and key accessible only by the investigators.

The target population for the study consisted of adult males and females ≥ 18 years of age diagnosed with diabetes, hypertension and CKD who were followed up at the KNH renal and diabetic clinic. Patients recruited had been on either losartan or enalapril therapies for a minimum period of twelve

months continuously. Patients who were either on renal replacement therapy or had undergone a renal transplant or pregnant were excluded from the study. Universal sampling of all eligible files was then done. Data were abstracted using a designed data collection tool.

For data analysis and interpretation, chronic kidney disease was defined as the presence proteinuria and GFR of less than 60ml/min/1.73m² over a 3 month period or by clinician diagnosis. Proteinuria was defined by a positive dipstick urinalysis of >1 or $+1$. The doubling of the serum creatinine concentration was defined as the first serum creatinine value that was twice the baseline value.

Outcomes of interest: The main outcomes of interest were doubling of baseline serum creatinine and changes in the level of proteinuria. The independent variables included age, gender, diabetes mellitus, hypertension, duration of illnesses, concurrent medications, smoking and alcohol habits, types of antihypertensives and patient adherence. Confounding variables included the use of nephrotoxic drugs, co-morbidities that may have caused renal failure and use of multiple antihypertensives.

Data analysis: Descriptive data analysis was carried out on all variables. The mean and median were calculated as the measures of central tendency. The range and interquartile range (IQR) for continuous variables was reported. For all categorical variables, the proportionate composition and the 95% confidence interval were reported.

Inferential tests such as the T- test, ANOVA and Chi Square were used to compare characteristics across the two arms. The 95% confidence interval for mean difference across the two independent groups was calculated.

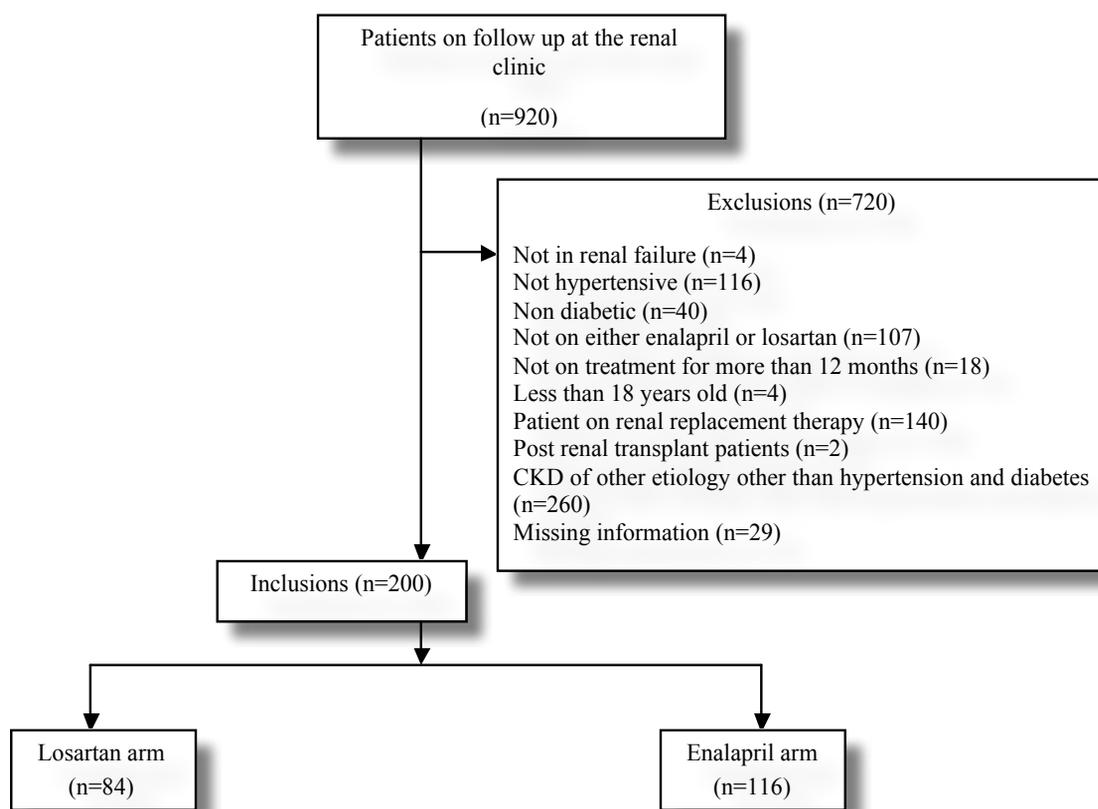
Survival data analysis was done using the Kaplan Meier method. Time to doubling of baseline serum creatinine was compared across study arms using the Log rank test. Associations were measured by the determination of the hazard ratio (HR).

Confounding was controlled for using the Cox regression models. Potential confounders were identified from the independent variables by a manned forward step wise modeling approach. IBM SPSS version 20 was used for these analyses. P values below 0.05 were considered statistically significant for all analyses.

RESULTS

Study cohort: We sampled 920 patients with CKD, of whom 200 met the eligibility criteria. Reasons for exclusions are shown in Figure 3.1.

Figure 1
Consort diagram of patient cohort eligibility and reasons for exclusion



Socio-demographic characteristics of the study population:

The patient gender ratio was approximately 1:1 (Table 1). Median age for all the patients was 63 years (range: 18-95 years). More than three quarters of the patients were above 50 years of age. Median age for patients who used enalapril regimen was 61 years (range: 51-70 years). This was significantly lower compared to the age of patients who used losartan regimen (median age: 65 years, range: 57-71 years), ($p=0.044$).

Medical history and baseline renal parameters of the study population:

At diagnosis, 37.0% of the patients were at stage 3 of renal failure and a cumulative percentage of 33.5% were at stage 4 and 5 (Table 2). A greater proportion of the participants had been in renal failure for 3-4 years (34.5%). At diagnosis, the median baseline serum creatinine value was $165 \mu\text{mol/L}$ (IQR: 105-277) while the baseline protein in urine was not detectable in 41% of the study population.

Table 1
Socio-demographic characteristics of the study population

Variables	Total (N=200)	Enalapril (n=116)	Losartan (n=84)	p-value
<i>Gender; n (%)</i>				
Female	101 (50.5)	58 (50.0)	43 (51.2)	0.868
Male	99 (49.5)	58 (50.0)	41 (48.8)	
<i>Age in years; Median (IQR)</i>				
<=50 years	33 (16.5)	25 (21.6)	8 (9.5)	0.024
>50 years	167 (83.5)	91 (78.4)	76 (90.5)	
<i>Marital status; n (%)</i>				
Single	21 (10.5)	17 (14.7)	4 (4.8)	0.067
Married	173 (86.5)	95 (81.9)	78 (92.9)	

Once married	6 (3.0)	4 (3.4)	2 (2.4)	
Highest level of education; n (%)				
Informal	23 (11.5)	17 (14.7)	6 (7.1)	0.369
Primary level	80 (40.0)	43 (37.1)	37 (44.0)	
Secondary level	73 (36.5)	43 (37.1)	30 (35.7)	
Tertiary level	24 (12.0)	13 (11.2)	11 (13.1)	
Use of alcohol; n (%)				
Yes	19 (9.5)	15 (12.9)	4 (4.8)	0.052
No	181 (90.5)	101 (87.1)	80 (95.2)	
Cigarette smoking; n (%)				
Yes	16 (8.0)	11 (9.5)	5 (6.0)	0.364
No	184 (92.0)	105 (90.5)	79 (94.0)	

Table 2
Past medical history and baseline renal parameters of the study population

Variables	Total (N=200)	Enalapril (n=116)	Losartan (n=84)	p-value
Type of diabetes; n (%)				
Type 1	19 (9.5)	16 (13.8)	3 (3.6)	0.015
Type 2	181 (90.5)	100 (86.2)	81 (96.4)	
Duration of diabetes; n (%)				
0-24 months	13 (6.5)	10 (8.6)	3 (3.6)	
25-48 months	12 (6.0)	10 (8.6)	2 (2.4)	
49-72 months	23 (11.5)	14 (12.1)	9 (10.7)	0.174
72-96 months	17 (8.5)	10 (8.6)	7 (8.3)	
>96 months	135 (67.5)	72 (62.1)	63 (75.0)	
Duration of hypertension; n (%)				
0-24 months	24 (12.0)	19 (16.4)	5 (6.0)	
25-48 months	22 (11.0)	14 (12.1)	8 (9.5)	
49-72 months	29 (14.5)	17 (14.7)	12 (14.3)	0.072
72-96 months	29 (14.5)	19 (16.4)	10 (11.9)	
>96 months	96 (48.0)	47 (40.5)	49 (58.3)	
Baseline Stage of renal failure; n (%)				
Stage1	18 (9.0)	8 (6.9)	10 (11.9)	
Stage2	41 (20.5)	24 (20.7)	17 (20.2)	
Stage3	74 (37.0)	44 (37.9)	30 (35.7)	0.584
Stage4	38 (19.0)	25 (21.6)	13 (15.5)	
Stage5	29 (14.5)	15 (12.9)	14 (16.7)	
Duration since diagnosis of renal failure (years); n (%)				
≥ 7	36 (18.0)	24 (20.7)	12 (14.3)	
5-6	52 (26.0)	31 (26.7)	21 (25.0)	
3-4	69 (34.5)	41 (35.3)	28 (33.3)	0.314
1-2	43 (21.5)	20 (17.2)	23 (27.4)	

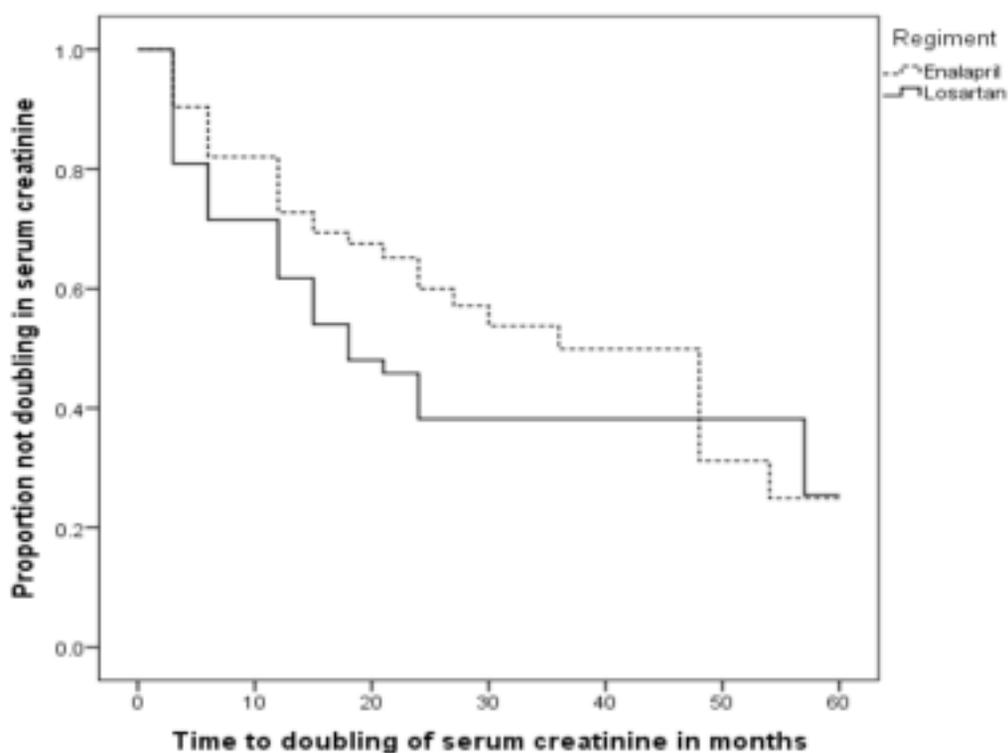
Baseline Serum Creatinine in $\mu\text{mol/L}$; Median (IQR)	165 (105 – 277)	171 (116 – 277)	154 (100 – 268)	0.550
Baseline proteinuria mg/dl; n (%)				
<30	89 (44.5)	49 (42.2)	40 (47.6)	
30	27 (13.5)	23 (19.8)	4 (4.8)	
100	33 (16.5)	18 (15.5)	15 (17.9)	0.021
≥ 300	51 (25.5)	26 (22.4)	25 (29.8)	
Protein; n (%)				
Absent	82	(41.0)	47	(40.5)

Incidence of doubling of serum creatinine: Survival probability at first doubling in serum creatinine decreases from 1.000 to 0.240 in a span of 1 to 57 months. Median time to doubling of serum creatinine was 24 months.

Survival probabilities were compared between different treatment arms. Figure 3.1 presents a comparison of survival probabilities to 1st doubling of Serum Creatinine between treatment arms. There was a significant difference in survival probabilities between the treatment arms ($p=0.046$).

Survival probabilities were compared between

Figure 2
Kaplan-Meier survival probability curve to first doubling of serum creatinine



Multivariate analysis: All factors identified to correlate with doubling of serum creatinine or use of enalapril or losartan at $p < 0.1$ were considered. Fourteen factors that were considered as candidates for the analysis included: regimen, date started on regimen, age in years, marital status, use of alcohol, type of diabetes, duration of hypertension, baseline protein in urine, use of amlodipine, carvedilol, cotrimoxazole, baseline stage of renal failure, baseline serum creatinine and baseline eGFR. Upon specifying backward conditional

method with removal at $p < 0.05$, twelve iterations were performed. The twelve successive iterations yielded to a parsimonious (reduced) model. Adjusting for baseline serum creatinine, the use of losartan was significantly associated with doubling in serum creatinine. It was established that a patient put on losartan regimen had 1.572-fold risk of experiencing doubling of serum creatinine levels compared to one on enalapril regimen (adjusted HR=1.572; 95% CI: [1.015, 2.434]; $p=0.043$).

Changes in the levels of proteinuria: Out of 200 study patients, 54 had complete data on the level of protein in urine for 15 months of follow-up. Stacked bar graphs were used to illustrate the changes in the proportions of patients at each level of proteinuria. A stacked bar graph for enalapril and losartan was

plotted as shown in Figures 3 and 4, respectively. There was no significant difference in the distribution of patients with different categories of protein in urine by treatment arms at most time points except at month 15.

Figure 3
Changes in the proportion of patients at different levels of proteinuria with time in the enalapril arm

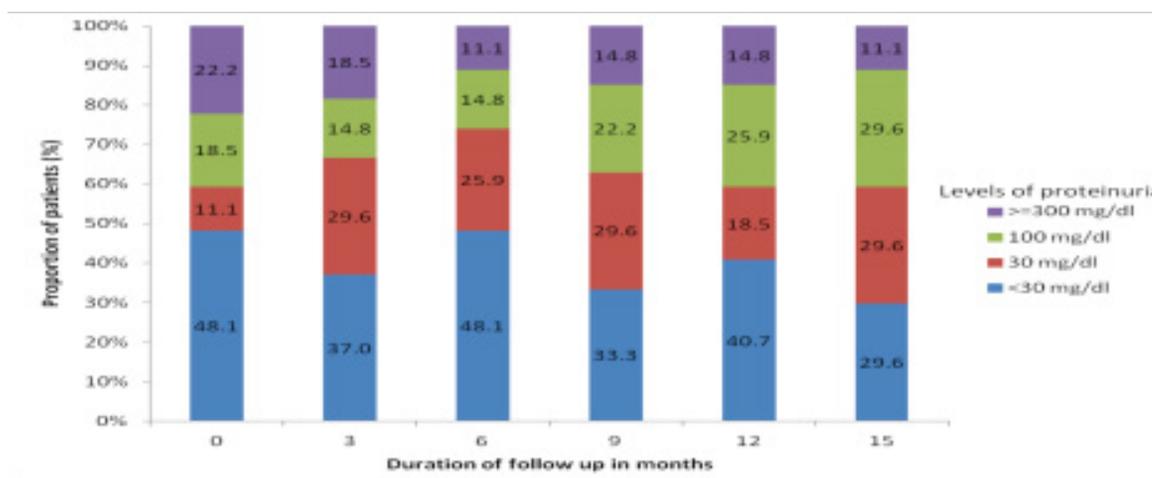
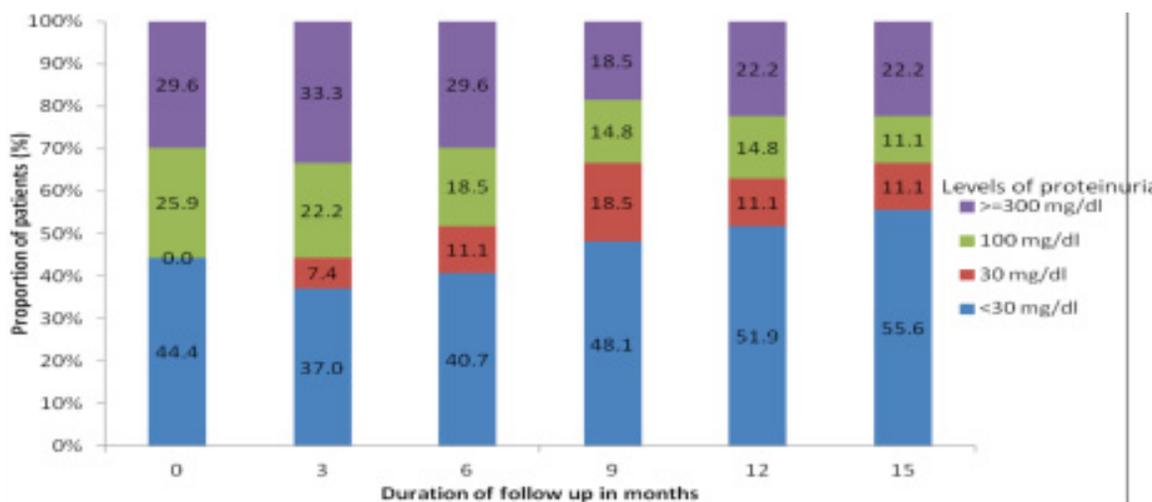


Figure 4
Changes in the proportion of patients at different levels of proteinuria with time in the losartan arm



Though the differences in the proportion of patients during follow up in the two arms were not statistically significant (month 0: $p = 0.301$, month 3: $p=0.162$, month 6: $p = 0.245$, month 9: $p = 0.587$, month 12: $p = 0.556$), comparisons between Figures 3 and 4 can be made. A significant difference was only noted at month 15 of follow up ($p=0.053$). In both the losartan and enalapril arms, the proportion of patients with ≥ 300 mg/dl of protein in urine decreased. The proportion of patients in the < 30 mg/dl range of protein in urine increased in the losartan arm while a decrease was observed in the enalapril arm between baseline and month 15 of follow up. Enalapril appeared to have a greater protective effect with greater magnitude of

reduction in the ≥ 300 mg/dl of protein in urine level.

DISCUSSION

Our results indicate that there is a statistically significant difference in the risk of doubling of serum creatinine between the two study arms. Patients on losartan had a 1.6 fold risk of experiencing a doubling of serum creatinine compared to those on enalapril. This risk is apparent after controlling for most confounders by the Cox regression model. The parsimonious model revealed that the baseline serum

creatinine concentration was predictive of doubling of the serum creatinine concentration.

Survival data analysis using Kaplan-Meier method revealed that the median time to the event was 24 months for both arms combined. However, a comparison of the two arms revealed that the losartan arm experienced this event at a median of 16 months of follow up whereas in the enalapril arm the experience was at 36 months ($p = 0.046$). This suggests that enalapril was superior to losartan in terms of preservation of renal function.

Our findings were not in agreement with the ONTARGET and DETAIL studies regarding the doubling of serum creatinine following treatment with ACE inhibitors or ARBs. The ONTARGET trial compared telmisartan and ramipril and concluded that the risk of doubling of serum creatinine was not statistically significant different between the two arms.⁽⁹⁾ Conclusions from the DETAIL study group, a head to head comparison of telmisartan and enalapril were similar.⁽¹⁰⁾ Our findings indicate that patients on an ARB (losartan) were at a higher risk of doubling of serum creatinine than those on an ACEi (enalapril). This can be interpreted to mean that enalapril is more renoprotective than losartan. The ONTARGET and DETAIL studies were done in predominantly caucasian populations. Our study was done in a black population. Perhaps this may also account to some degree for the apparent variations of results between those studies and this study. Furthermore, the specific drugs used in this study were different.

The changes in the levels of proteinuria did not differ across the enalapril and losartan arms for most of the follow up period till month 15 where it became significant ($p=0.05$). Patients on the enalapril based regimens had greater reductions in proteinuria at the $\geq 300\text{mg/dl}$ mark compared to those on losartan regimens. Our results concur with the argument that patients with higher levels of proteinuria above 1g per day at baseline or during follow up benefit most from therapy with ARBs or ACE inhibitors⁽⁹⁾.

The ONTARGET study during a comparison of the ACE inhibitor, ramipril and the ARB, telmisartan found that the decrease in urinary albumin excretion was less with telmisartan compared to with ramipril⁽⁹⁾. Lacourciere *et al.* on the other hand compared reduction of urinary albumin excretion between losartan and enalapril. After 52 weeks of follow up, the reduction in proteinuria from baseline was higher with enalapril than with losartan.⁽¹¹⁾ Our study concurred with those findings, even though there were no statistically significant differences in the changes in the levels of proteinuria between the two arms for most of the follow up period except month 15. We suggest that our findings relating to changes in the level of proteinuria be interpreted with caution.

We postulate that the differential effects observed

between the two drugs are related to their mechanisms of action. Both drugs not only block the RAAS, they also cause differential stimulation of the Kallikrein Kinin System (KKS) with the resultant renal effects.^(1, 12, 13) The beneficial effects of both ACE inhibitors and ARBs can be attributed in part to activation of the KKS. This may be mediated by enhanced synthesis of nitric oxide (NO) and prostacyclin, a prostaglandin (PG), which shifts the metabolism from mitochondrial respiration to glycolysis. NO and PG cause vasodilatation, prevent fibrosis and inflammation, reduce production of ROS and are anti-thrombotic. All these effects prevent the progression of diabetic nephropathy. Of the two classes of drugs, ACE inhibitors are more effective in enhancing the activity of the KKS⁽¹⁴⁾. It has been argued that even though ACE inhibitors were developed as RAAS blockers, they function primarily as stimulators of the kinins rather than ACE inhibitors^(14, 15). This argument would support our findings where patients on enalapril regimens had better preserved renal function compared to those on losartan regimens. Information is, however, lacking on the role of kinins on the intrarenal effects of ACE inhibitors and ARBs. Animal studies have demonstrated that kinins may cause efferent arteriolar vasodilatation, but this effect has not been demonstrated in humans putting doubt on the role of their role in reduction of proteinuria.⁽¹⁴⁾

A limitation of the present study, as is common with retrospective studies, is missing information, which eventually reduced the sample size thereby lowering the power of our study from 90% to 86%. The small sample size also may have contributed to the lack of statistically significant differences in the changes in the levels of proteinuria between the two arms. The variation of data on proteinuria which was largely due to the fact that most patients did not have the urinalysis test done regularly as requested by the physician may also have affected our results. Finally, this being a retrospective study also limited our ability to collect data on other key factors that may have contributed to the observed differences such as ethnicity and genetic polymorphisms.

CONCLUSION

The results show that patients who were on losartan based regimens were at a higher risk of experiencing a doubling of serum creatinine than those on enalapril based regimens.

We therefore recommend the use of enalapril based regimens as first line therapy in type 2 diabetic CKD patients with hypertension. The use of losartan as first line in RAAS blockade naïve patients should be discouraged based on the higher risk of decreased renal function. Prospective cohort studies or randomised controlled trials with larger sample

sizes are necessary in order to provide more evidence of the superior effects of ACE inhibitors especially in black populations.

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