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Original Research Article

Aliskiren and losartan study in non-diabetic CKD: a comparison of patients in the clinical trial versus the usual care group

Keng Thye Woo[1]*, Choong Meng Chan[1], Stephanie Fook Chong[2], Cynthia Lim[1], Jason Choo[1], Lina Choong[1], Suhail Mohamad[1], Han Kim Tan[1], Kok Seng Wong[1], Marjorie Foo[1]

[1]Department of Renal Medicine, [2]Department of Statistics and Epidemiology, Singapore General Hospital, Singapore

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***Correspondence:**
Prof. Keng -Thye Woo,
E-mail: woo.keng.thye@sgh.com.sg

ABSTRACT

Background: This is a comparative study of a 6 year retrospective analysis of the therapeutic efficacy and safety of Combined Aliskiren (150 mg a day) and Losartan (100 mg a day) in a Clinical Trial setting versus a Usual Care group of patients on Losartan (100 mg a day), Telmisartan (80 mg a day) and Combined Enalapril (10 mg a day) plus Losartan (100mg a day) in non-Diabetic Chronic Kidney Disease (CKD) patients. The objective of this study was to ascertain if there were any differences in the renal outcome of patients treated within a Clinical Trial setting versus a Usual Care setting. The study seeks to establish the relevance of having a Usual Care group as a comparator and whether its inclusion in the study would help to validate the findings in the Clinical Trial group
Methods: This is a 2nd Phase follow up study three years after the initial 1st Phase study in the Clinical Trial Group. Patients in the 2nd Phase study were those who continued to have proteinuria and were treated with Losartan 100mg a day. The 2nd Phase study seeks to document the incidence of remission of proteinuria following their initial 1st Phase therapy for proteinuria compared to those in the Usual Care group where treatment remained unchanged from year 1 to end of year 6. The rates of remission of proteinuria and improvement of renal function as well as associated comorbidities between the 2 groups are compared.
Results: Among the 154 patients in the Clinical Trial Group, 70/154 (45%) continued to have proteinuria, while 84/154 (55%) had no proteinuria (remission) compared to 41 (28%) in remission and 104 (72%) with continued proteinuria in the Usual Care group ($p<0.001$). There were more patients with hypertension and hyperkalaemia in the Clinical Trial group compared to the Usual Care group. Seven patients were in ESRF in the Usual Care group compared to only 3 in the Clinical Trial group but this difference was not significant. More patients in the Clinical Trial group compared to the Usual Care group had improvement in eGFR at the end of the 6 years ($p<0.001$).
Conclusions: This study shows that patients in a Clinical Trial setting do better than those in the Usual Care setting as they are more likely to have improvement in renal function with remission of proteinuria.

Keywords: Aliskiren, Chronic kidney disease, Comparison, Clinical trial versus usual care

INTRODUCTION

In this paper we compare the results of a study comprising 154 patients in a clinical trial (COMB A) and its 3 drug arms to test a combination dosage of Aliskiren versus two other competing drug arms to assess the safety and efficacy of the combined therapy in reducing proteinuria and retarding the progression of renal failure. The duration of this trial was terminated prematurely at the end of 3 years due to the adverse effects of Aliskiren (1). Aliskiren was discontinued and the trial proceeded for another 3 years to assess any legacy effects of

Aliskiren. For those patients who still had proteinuria they were treated with Losartan and for those who had remitted Aliskiren was stopped.

During these 6 years, the group of 145 patients from the remaining cohort of 312 patients (COMB 300)), not selected for the Aliskiren study were followed up as the "Usual Care" group (COMB B) to act as control for the clinical trial group in order to compare the renal outcome and comorbidities of COMB A versus COMB B to ascertain whether patients in a Clinical Trial group fared better than a usual care group.

The Altitude study based on a combination dosage of Aliskiren and ARB was terminated because of unfavourable reports which showed that patients treated with the combination dosage had higher incidence of hyperkalaemia and higher incidence of strokes and myocardial infarction.[1,2] Subsequently, the health sciences authority [HSA] in Singapore and the European Medicines Agency also issued an advisory against the use of combination dosage of Aliskiren and ARB.[3,4] When our 1st Phase I study was terminated, the results of which have been published, patients however continued on the study (2nd phase) first to see if there were any legacy effects of the 1st phase therapy with combination therapy of combined Aliskiren and Losartan and secondly to study the effects of stopping therapy on proteinuria.[5]

The patients in this group designated the "Clinical Trial Group" was compared with another group, designated the "Usual Care Group" to ascertain if there were any differences in the renal outcome in terms of renal function and proteinuria as well as other related comorbidities. The addition of a comparator arm to the clinical trial as standard of care would allow us to test whether such a comparator group would help to increase the relevance and validity of the findings in the Clinical Trial group with the assumption that a clinical trial should observe standards superior if not at least equivalent to that of usual care without causing any harm to the clinical trial subjects.[6] The principles and indications for drug therapy in both the clinical trial and the usual care group were adhered to and considered as evidence based guidelines in the therapy of patients with stage 3 chronic kidney disease (CKD).[7] These guidelines are the designated KDIGO guidelines.[8,9]

METHODS

In a database comprising 312 patients (COMB 300) with CKD attending our renal clinic, 154 patients with CKD due to chronic glomerulonephritis and not due to diabetic nephropathy, hypertensive nephrosclerosis, lupus nephritis or Henoch Schonlein nephritis were recruited for the study (COMB A). From 2007 to July 2012, data of these 312 patients (COMB 300) were examined for the purpose of a retrospective study. Non biopsied CKD patients formed the bulk of our clinical practice and were more readily recruited. For purposes of standardisation of the study, we decided to recruit only non-biopsied patients into the study. In this new database for the purpose of this study, the database of 154 patients (COMB A) were selected, among which 51 patients were treated with combination therapy using an ARB (Losartan) and Aliskiren (a), 52 patients were treated with Aliskiren alone (b) and the remaining 52 patients were treated with ARB (Losartan alone) (c). As this was a retrospective study involving only patient medical records, waiver of informed consent was obtained for all patients from the hospital's Institutional Review Board (IRB). Entry criteria included those patients who had been treated on the above drugs for at least 36 months within the 5 years period; other criteria included proteinuria of 1 gram or more and or CKD Stage 3 at the start of the 36 months period.

We had identified these 154 patients (COMB A) for a 2nd Phase study with the intention of an additional 3 year follow up with regards to documenting the proportion of patients where proteinuria disappeared completely (total urinary protein, [TUP] $\leq$0.2 gm/day) for the next 3 years without any treatment (remission). For the other patients who continued to have proteinuria they were all treated with Losartan 100 mg a day as a standard therapy and continued to be assessed every 6 months to completion of 3 years 2nd phase follow up study (continuing proteinuria group).

The remainder of the patients (158) (COMB B) among the 312 patients formed the control group for the study. These 158 were patients who did not meet the criteria for inclusion in the earlier 154 patients were designated the "Usual Care Group". Among these 158 patients designated the usual care group, 12 patients were not suitable as they had incomplete case records and 1 patient was lost to follow up, leaving 145 patients in the usual care group (COMB B). Among these 145 patients, 57 patients were on Losartan 100 mg a day (d), 39 were on Telmisartan 80 mg a day (e) and of the remaining 49 patients, 39 were on Losartan 100 mg and Enalapril 10 mg a day and the other 10 patients were on Losartan 100 mg and Ramapril 4 mg a day, collectively they were designated the Losartan and Enalapril group (f) in the study.

Study design

All 154 patients on the clinical trial database had the following investigations documented at six monthly intervals: serum creatinine, eGFR and total urinary protein (TUP). Serum creatinine was quantitated with alkaline picrate and TUP was quantitated by biuret agent. Estimated Glomerular filtration rate (eGFR) was estimated using the Cockcroft Gault formula for eGFR. Decrease in eGFR was expressed as ml of eGFR loss per year over the 6 year duration from time of entry to exit of the trial. Improvement in eGFR was taken as the positive difference between the entry eGFR and the exit eGFR over the study period. End stage renal failure was equated

with decline of eGFR to CKD stage 5 with eGFR less than 15 ml/min/year. The primary end points were stage 5 CKD or end stage renal failure. The secondary end points were reduction of proteinuria by 50% and change in eGFR.

The 145 patients in the usual care group also had all the above tests conducted routinely at their clinic visits at 6 monthly intervals. They were prescribed the standard drugs of angiotensin receptor blockers (ARB) like Losartan and Telmisartan or angiotensin converting enzyme inhibitors (ACEI) like Enalapril and Ramipril during their clinic consultations. This group of patients were not prescribed Aliskiren where the cost of the drug was not subsidised. Aliskiren was then considered a new or retail drug and patients would have to pay the full cost to be on Aliskiren compared to the usually provided subsidised drugs where patients pay only 20% of the cost price.

Sample size

Sample size calculation was based on the proportion of patients achieving 30% decrease in TUP with treatment of normal dose Aliskiren or normal dose Losartan. A second sample size calculation was done to compare the rate of 30% TUP decrease between a combination dose of ARB Losartan plus Aliskiren and Aliskiren alone. Assuming that the rate of TUP decrease to be 30% in the Normal dose ARB and Normal dose Aliskiren and 60% in the combination dose of ARB plus Aliskiren, the number of patients required in each group was 49 for a 2-sided test with alpha=0.05 and power of 80%. We expected the effects of combination dose of ARB plus Aliskiren to be about the same as that of high dose ARB. Sample size for this clinical trial group is 154.

The sample size for the patients in the usual care group was 145 with 57 patients in the Losartan group, 39 in the Telmisartan group and 49 in the combined Losartan and Enalapril group. Coincidentally they were about the same in sub group sizes, except for the Telmisartan of 39 patients which did not fulfil the required numbers.

Hence this study has its limitations since it is not an appropriately designed matched control study.

Statistical methods

SPSS 10.1 for Windows was used for all analysis. Results were expressed as mean±SD or median (range) or count (%). For univariate analysis, Pearson's chi-square test was used for comparing categorical data and ANOVA for comparing numeric data between the clinical trial and the usual care group as well as both their 3 treatment arms. ANOVA was followed by multiple comparisons with Student-Newman-Keuls (SNK) range test whenever statistical significance was found between these 2 groups and their respective 3 treatment arms.

Next, a doubly multivariate ANOVA (MANOVA) with repeated measures was used to test the effect of drug treatment on both eGFR and total urine proteinuria (TUP) for the 2 groups of Clinical Trial and Usual Care patients as well as their respective 3 treatment arms. The dependent variables were eGFR and TUP measured at 7 time points, namely baseline and thereafter every year of the 6 years of the study. The between-subject factor was treatment group with 3 levels corresponding to combination dose of Losartan and Aliskiren, Aliskiren alone and Losartan alone. This was repeated for the other 3 patient arms of Losartan alone, Telmisartan alone and Losartan plus Enalapril for the usual care group. Adjustment was made for the covariates of average systolic BP and average diastolic BP. Average blood pressures were calculated by taking the mean of all blood pressures while on medication (mean of blood pressures from year 1 to year 6). Within MANOVA, the effect of combination dose of Aliskiren and Losartan on the outcomes of eGFR and TUP was compared with each of the other drug dosage groups by simple contrast comparison testing. Similarly, repeated contrast testing was done to obtain and compare the loss in eGFR in each year between the various drug groups. The same MANOVA was repeated for the three patient arms of Losartan alone, Telmisartan alone and Losartan plus Enalapril in the Usual Care group.

Plots of mean values of eGFR and TUP adjusted for covariates of systolic BP and diastolic BP were presented; so were the contrast estimates, their corresponding 95% confidence intervals and p-values for the comparison of eGFR and TUP between the levels of interest of the 3 drug groups in both the Clinical Trial and Usual Care groups.

RESULTS

Table 1 compares the demographic and clinical profile of patients in the clinical trial and the usual care group.

There were more female patients (64%) in the clinical trial group compared to more male patients (57%) in the usual care group ($p<0.001$). The patients in the clinical trial group were also younger (52±11 years) compared to those in the usual care group (58±11 years) ($p<0.001$). There were more patients with hypertension (47%) in the clinical trial group compared to those in the usual care group (31%) ($p<0.001$). The incidence of hyperkalaemia was higher among those patients in the clinical trial group (26%) compared to those in the usual care group (16%) ($p<0.001$). There was no difference in the incidence of IHD and hypercholesterolemia between the 2 groups.

The BP levels, systolic and diastolic over the 6 years for the clinical trial and usual care group are displayed in Figures 1 and 2 respectively. There were no significant differences between the 2 groups throughout the 6 years. There was a significant decrease in both the systolic and diastolic BP between the BP of year 1 and year 6 within the group themselves but no difference in the BP between

the clinical trial and usual care groups, both groups had well controlled BP as shown in Figures 1, 2 and Table 1.

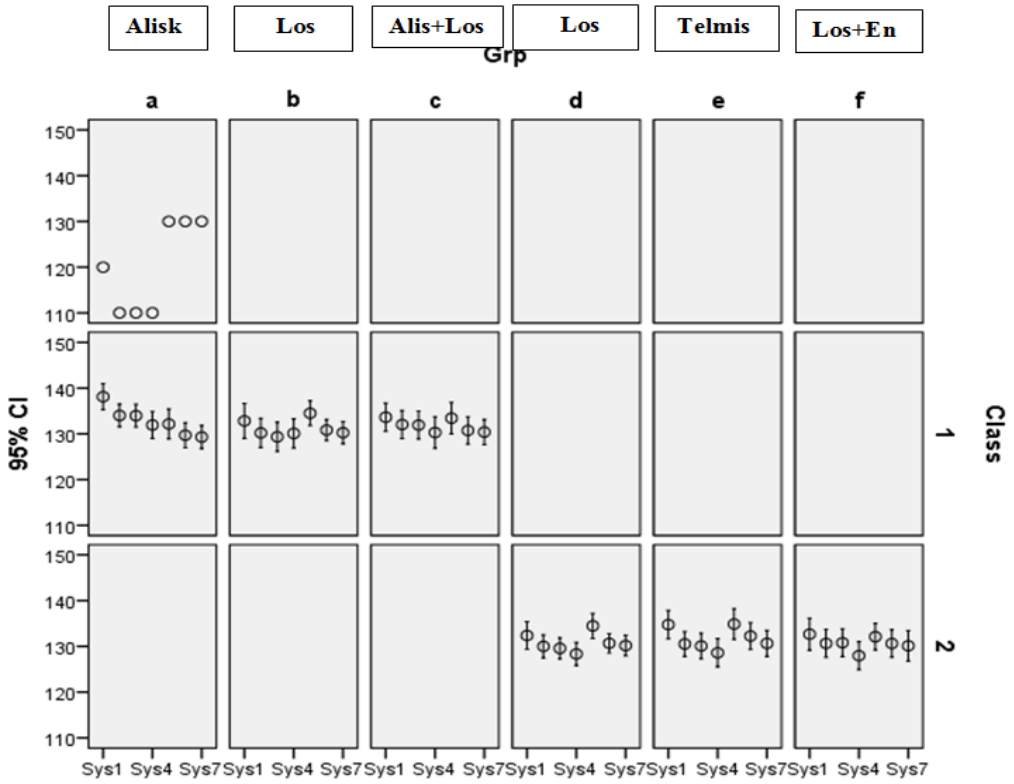

Figure 1: Distribution of systolic blood pressure (mmHg) over the years by combination of clinical trial group and usual care group at the end of trial from year 1 to 7.

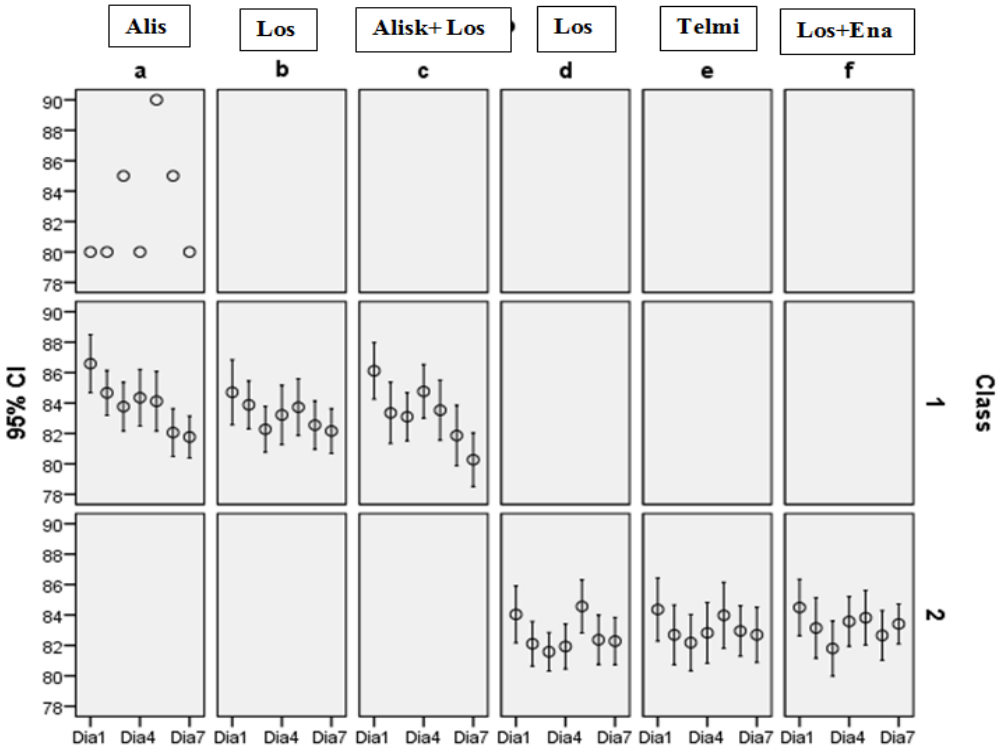

Figure 2: Distribution of diastolic blood pressure (mmHg) over the years by combination of clinical trial group and usual care group at the end of trial from year 1 to 7.

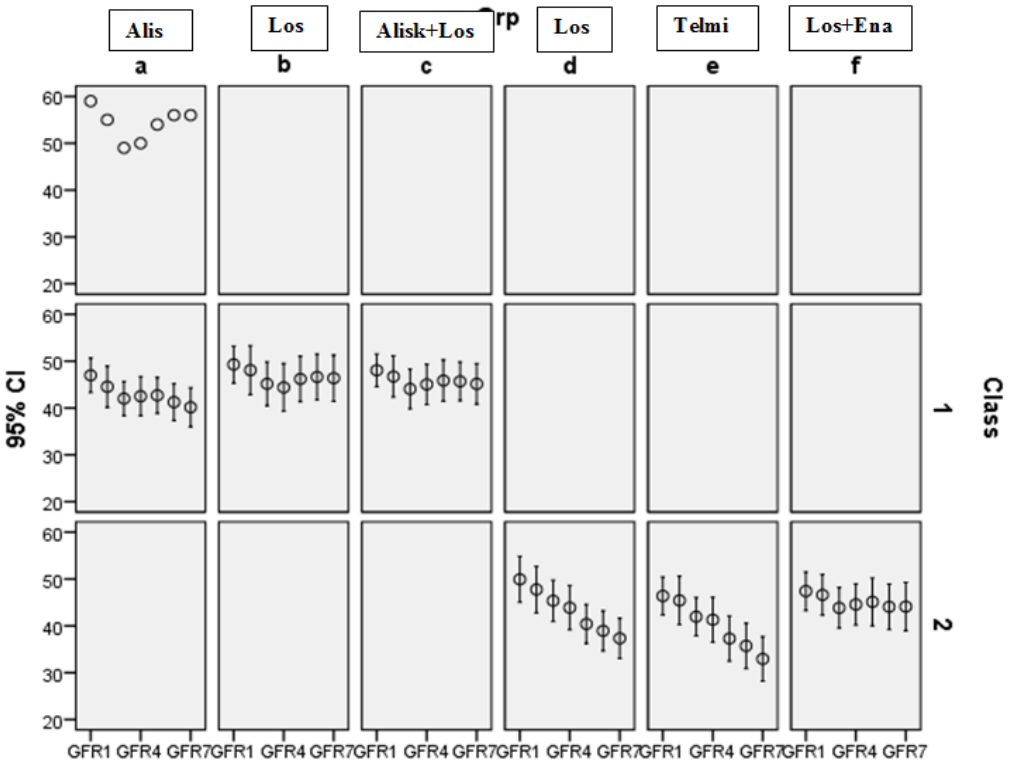

Figure 3: Distribution of eGFR over the years by combination of clinical trial group and usual care group at the end of trial from year 1 to 7.

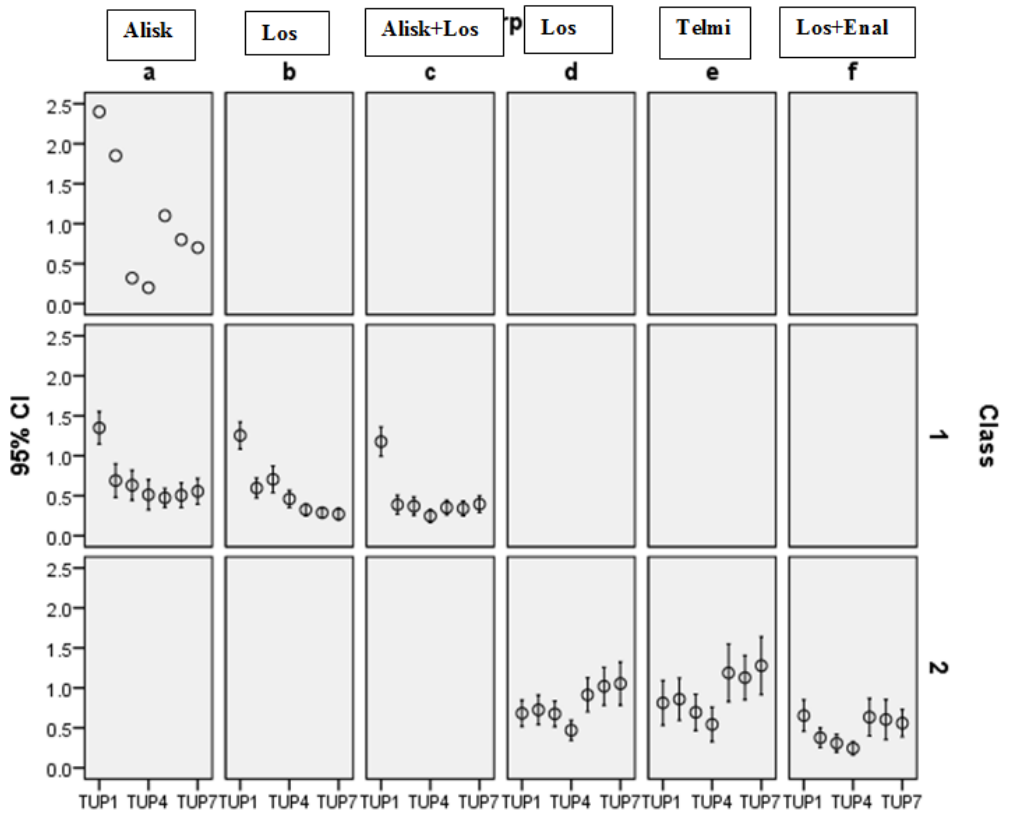

Figure 4: Distribution of proteinuria over the years by combination of clinical trial group and usual care group at the end of trial from year 1 to 7.

Table 1: Comparing demographic and clinical profile of patients in clinical trial and usual care group (year 1 to 6).

	Clinical trial group n=154	Usual care group n=145	*P value
Sex (F: M) count (%)	98:56 (F-64%:M-36%)	62:83 (F-43%:M-57%)	0.001
Age at diagnosis (Years)	52±11	58±11	0.001
Duration of trial (Months)	73±2	73±2	0.78
Comorbidities, count (%)			
Hypertension	72 (47%)	49 (31%)	0.001
Hypercholesterolaemia	80 (52%)	77 (53%)	0.81
IHD	25 (16%)	30 (20%)	0.21
Hyperkalaemia	41 (26%)	23 (16%)	0.001
EGFR (ml/min)			
Year 1	48±13	48±12	0.99
Year 6	44±16 (p<0.001)	38±17 (p<0.001)	0.005
Urinary Protein (gm/day)			
Year 1	1.3±0.7	0.74±0.7	0.001
Year 6	0.43±0.4 (p<0.001)	0.94 (p<0.001)	0.81
Blood Pressure (mmHg)			
Systolic, Year 1	135±12	133±11	0.20
Systolic, Year 6	129±9 (p<0.001)	130±10 (p<0.015)	0.96
Diastolic, Year 1	86±7	84±6	0.55
Diastolic, Year 6	81±6 (p<0.001)	83±5 (p<0.039)	0.89
Improvement in eGFR	42 (27%)	33 (23%)	0.001
CKD, Year 1	3.0±0.3	0.35±0.3	0.61
CKD, Year 6	2.9±0.6 (p<0.001)	3.2±0.8 (p<0.001)	0.28
Number with ESRF	3	7	0.33
Response:			
Remission "x" n=	70 (45%)	41 (28%)	0.001
Continuing Proteinuria "z", n=	84 (55%)	104 (72%)	

Continuous data are presented as mean±SD and categorical data as count (%).

There was a significant decrease in systolic BP before and after the trial for both groups p<0.001 for clinical trial group and p<0.015 for the usual care group (Figure 1).

There was a significant decrease in diastolic BP before and after the trial for both groups, p<0.001 for clinical trial group and p<0.039 for the usual care group (Figure 2).

There was a significant decrease in eGFR before and after the trial for both groups p< 0.001 for clinical trial group and p<0.001 for the usual care group. Comparison of the eGFR shows that the usual care group had a more significant decrease in eGFR at year 7 compared to the clinical trial group (p<0.005) (Figure 3).

Proteinuria between the two groups were significantly different, being more in the clinical trial group compared to the usual care group (p<0.001). At the end of the trail there was a significant decrease in proteinuria for the clinical trial group, p< 0.001 but for the usual care group, proteinuria increased significantly (p<0.001) (Figure 4).

The eGFR significantly was lower for both the clinical trial and the usual care group when compared before and after the trial with the eGFR in the usual care group significantly lower than the clinical trial group at the end of year 6 (p<0.005) as shown in Table 1 and Figure 3. The TUP in both the clinical trial and usual care group was also significantly different at the end of year 6 compared to year 1 as shown in Table 1 and Figure 4, but whilst the TUP was lower in the clinical trial group, in the usual care group the TUP was higher between year 1 and year 6 (p<0.001) as shown in Table 1. However, comparing the initial TUP at Year 1 between the two groups, the TUP of the clinical trial group was significantly higher than that of the usual care group (p<0.001), (Table 1).

There were 3 patients with ESRF in the clinical trial group compared to 7 in the usual care group but this difference was not significant (Table 1). Similarly, more patients had remission of proteinuria (TUP ≤0.2 gm/day) in the clinical trial group (n=70) compared to those in the usual care group (n=41) and this difference was significant (p<0.001).

A Chi square analysis of the clinical trial group and the usual care group comparing with the proportion (%) of patients in each of the groups, show that those patients in the clinical trial group had more remission (45%), and

lesser number of patients with continuing proteinuria (55%) ($p<0.001$) compared to the usual care group as shown in Table 1.

DISCUSSION

In this study comparing two groups of patients, one in a clinical trial setting compared to another group in the usual care setting; patients in the clinical trial group were younger and there were more females compared to the predominantly male and much older patients in the usual care group. These two groups are therefore disparate in regards to sex and age which may affect the outcome of the progression of the eGFR during the trial. We are cognizant of this and maintain a conservative approach with regards to the results of the study.

At entry into the study the usual care group had proteinuria less than a gram a day compared to those in the clinical trial with more than 1 gram a day. This arose because most of the patients with TUP >1 gm were recruited into the clinical trial group leaving the rest from the 312 patients to form the usual care group. This would be another factor influencing the outcome of the study. These disparities between the two groups illustrate the difficulties we faced in the choice of a usual care comparator group.

The eGFR in both groups were comparable, stage 3 CKD on entry into the study, but at the end of 6 years whilst the clinical trial group had improvement in proteinuria, those patients in the usual care group had worsening of proteinuria with a greater loss of eGFR over the 6 years, resulting in 7 patients with ESRD compared to 3 in the clinical trial group. There could be various reasons for this difference in outcome between the clinical trial and usual care group, some of which have been mentioned earlier. We believe that one of the main reasons for the disparity in the outcome could be drug compliance in the usual care group. In the clinical trial group, a trial coordinator would monitor those patients on Aliskiren, a new drug, to document its side effects as well as to ensure compliance with drug taking whereas for the usual care group, patients were not monitored and some patients may not be so compliant in their drug ingestion. Another reason could be that, perhaps women, especially the younger ones in the clinical trial group are naturally more attentive and therefore less forgetful and more compliant with drug ingestion.

However in terms of comorbidities, those in the clinical trial group had a higher incidence of hypertension as well as hyperkalaemia compared to the usual care group. The usual care group had lower incidence of hypertension when compared to the clinical trial group as those patients in the Losartan and Enalapril arm of the usual care group were prescribed Enalapril mainly for control of hypertension rather than for proteinuria for which Losartan was prescribed. Patients in the Losartan and Enalapril arm of the usual care group had the highest incidence of hypertension.

This study involves an open labelled, non- randomized clinical trial to assess the safety and efficacy of combination therapy of Aliskiren and Losartan where it was compared with two competing drugs arms, Losartan alone and Aliskiren alone. The whole clinical trial group was compared with a usual care group where patients were on usually prescribed standard drugs involving a combination arm on Losartan and Enalapril, Losartan alone and Telmisartan alone. In addition those selected for the clinical trial were willing to pay for the new medicine Aliskiren for treatment of proteinuria resulting from CKD. The usual care group were the patients treated with the standard drugs where they had 80% of the cost subsidized by the government (Ministry of Health).

But despite the eGFR being comparable in both groups in year 1 with the usual care group having lesser TUP, by the end of the trial at year 6, whilst the TUP in the clinical trial group was significantly reduced as a result of therapy, TUP in the usual care group increased with lesser number of patients in remission and more patients with ESRD.

This study illustrates that patients recruited for a clinical trial had better renal outcome compared to those in the usual care group. There could be various reasons for this apart from the disparity between the two groups, sex and age being considered earlier as well as affordability for the new drug. For the clinical trial patients there was a clinical trial coordinator who would monitor the trial patients to ensure that they take their medication appropriately (drug compliance) and were also specifically asked about the occurrence of any adverse effects due to the drugs. The usual care patients do not have this monitoring as they were taking standard drugs and there was no one to monitor their drug compliance. This phenomenon has been alluded to in the paper by Young et al which compares pharmacist managed anticoagulation with usual medical care in a family medicine clinic where those patients managed by a pharmacist fared better compared to those on the usual medical care.[10]

For the usual care group, the patients were also not randomised and the study was retrospective. Like the clinical trial group these patients were managed by the same team of doctors and nurses. The only difference was that they were not on Aliskiren and therefore were not monitored during the first 3 years for drug compliance and adverse effects of Aliskiren. But from year 4 to year 6 both groups were no longer monitored as patients in the clinical trial group had stopped Aliskiren. Both groups had attended the 6 monthly clinic visits with their 6 monthly routine laboratory investigations and other tests as when required. They had access to clinic staff for various aspects of care, including access to dieticians,

medical social workers, pharmacists, dialysis and transplant coordinators.

Both groups had their clinic physicians assess the results and managed their drug therapies. The dosage recommendation was based on evidence based guidelines. Serious side effects were reported by nurses and physicians.

This study though laden with inadequacies because of its nonrandomised and retrospective nature is far from the ideal "prospective randomised control trial, double blinded including placebo".[6,11] A randomised double blind clinical trial would be the gold standard for evaluating a new therapeutic intervention. However, in such an ideal trial, the physician may become too aware of the trial and become more vigilant about monitoring, yet the best trial is the "prospective randomised control trial".[6,11] The next best would be a well designed retrospective study where two groups are comparable so as to reduce selection bias.[6] Many clinical trials do not have a usual care arm and the patients are randomised to 2 or 3 competing strategies. Others use 'selected control groups" widely regarded as the 'standard approach". Many trials have asked important research questions without using a usual care or control group. Would they have been more informative or "safer" if a usual care or control group had been used? According to Thompson and Schoenfeld" the design should fit the purpose and usual care could be considered for blinded trials of experimental drugs and devices or for treatment strategies that are not part of usual-care practices".[6]

The consensus is that there may be scientific, ethical and practical reasons for having an arm in a clinical trial that employs a usual care group.[11] If a researcher hypothesises that a new intervention is better than or at least equivalent to current clinical practice, then one arm should reflect usual care. A usual care arm might improve relevance, external validity or practicality of the study. However there are challenges formulating comparison groups to represent usual care. Dawson et al in an open access article based on an NIH funded meeting in 2005 on" considering usual care in clinical trial design" reported 5 types of difficulties in defining a comparison group: 1. Disputes about evidence, 2. Low level of utilisation of best methods, 3. Trade- offs relating to physicians' and patients' preferences for different treatment, 4. Insufficient pre-existing evidence base to guide treatment selection and 5. Individually customised medical care for conditions with no standard practice guidelines.

Hence, the choice of a comparison arm representing usual care can be challenging when there is no clear cut uniform standard of care. In the case of a new drug, then a usual care arm would help to decide if the new drug is superior to that in the clinical trial. Ultimately, the goal should be to answer why a treatment is effective, by how much versus a defined comparison or usual care arm and the group of patients it is likely to benefit.[13] For our study using the usual care group, in a modest way, despite the many disadvantages due to various bias in the trial design we have shown that within the usual care or comparator group, uncontrolled proteinuria is associated with loss of eGFR and renal failure as opposed to the clinical trial group which shows that control of proteinuria helps to preserve renal function. The usual care group has helped to improve the relevance as well as validate the findings in the clinical trial group. Whereas the clinical trial group has shown that effective control or reduction of proteinuria in CKD patients would help to preserve renal function and prevent renal failure which is the crux of the problem faced by countless number of patients afflicted by and bearing the heavy burden of CKD. Hence, the usual care group may reveal inadequacies of usual care practice. A usual care group will reinforce the reason for the emphasis on clinical trials observing high standards of medical care to ensure delivery of best practices to trial subjects.[12]

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