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ROLE OF ANGIOTENSIN RECEPTOR BLOCKERS IN DELAYING PROGRESSION OF DIABETIC NEPHROPATHY IN NORMOTENSIVE TYPE 2 DIABETES MELLITUS PATIENTS: AN OPEN-LABEL RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Background: Diabetic nephropathy is the most common cause of end-stage renal disease worldwide, and while we know ARBs to be renoprotective in diuretic treated diabetic patients with hypertension, the evidence for DRR in normotensive patients is uncertain. We report a prospective, open-label randomized controlled trial of patients with type 2 diabetes mellitus and new diabetic nephropathy living in a normotensive sustainable lifestyle intervention, showing that renoprotective effects from ARBs should be extended to those living in a normotensive state.

Methods: 84 normotensive patients were **randomized** to receive either increasing renoprotective doses of ARB (n=42) or standard care without RAS blockade (n=42). Serum creatinine, creatinine clearance (eGFR), and urine protein/creatinine ratios were determined at baseline and again at 12 months after therapy.

Results: Patients randomized to ARBs had significantly improved eGFR compared to the control group greater differences in terms of renal function were increased 4.8 ml/min/1.73m2 difference compared with no increase in eGFR in non ARB treatment group p=0.03). These patients also had significantly less proteinuria, (media of reduction in PCR 0.42 vs 0.08 median PCR reduction p=0.01) normotensive patients benefited most if they had baseline microalbuminuria and had the greatest overall benefit.

Conclusion: This open-label RCT provides evidence that ARB therapy offers significant renoprotection to normotensive type 2 diabetes patients.

1. INTRODUCTION

Diabetes affects about 20–40% of patients with diabetes mellitus [1] and is the most common cause of ESRD in developed countries. There is current interest in the role of AGEs (advanced glycation end products) and diabetic nephropathy [2]. The mechanisms that contribute to this might include, rapid glomerular hypertension/glycosuria occurring early in diabetes, leading to hyperfiltration injury, and capacity for recapture of loss is diminished as endothelial injury in part from activation of the renin-angiotensin system furthers inflammation/expression of profibrogenic (and damage to the endothelium). Angiotensin receptor blockers (ARBs) have been efficacious in delaying progression in the cohort of diabetic type 2 diabetes patients.The landmark RENAAL and IDNT trials established ARB's as first line therapy for renoprotection in this population showing significant reductions in doubling of serum creatinine, progression to end stage renal disease and death [3,4]. However, these benefits were demonstrated in populations whereby lowering blood pressure per se may have contributed to a significant portion of the renal outcome.

The role of ARB's specifically in normotensive patients is less well defined. Up to 30-40% of patients with type 2 diabetes and incipient nephropathy will present with normal blood pressures at diagnosis [5]. Current guidelines give no helpful advice on starting RAS blockade in this subgroup. New evidence suggests that inhibition of the RAAS produces organ-protective effects (for kidney, heart and vasculature) uncoupled from blood pressure lowering that result from attenuation of intrarenal angiotensin II, reduced transforming growth factor-beta expression, and amelioration of glomerular capillary pressure [6].

In a systematic review, Strippoli and team showed ACEi's to show benefit in primary prevention in normotensive patients; the evidence for ARB's not as strong [7]. The IRMA-2 trial however, showed irbesartan 300 mg daily reduced progression to overt nephropathy by 70% in normotensive type 2 diabetic patients with microalbuminuria independent of change in blood pressure [8].

The equipoise regarding ARB use in normotensive diabetic patients is due to several factors. Most trials, as noted above, have always enrolled large proportion of individuals who were hypertSecond, the degree of blood pressure-independent renoprotection is still uncertain, with some meta-analyses indicating that blood pressure reduction mediates much of the observed benefit [9]. Thirdly, there are potential adverse effects such as hyperkalemia and acute kidney injury, which should be weighed against the risks inherent in these normotensive patients. Given that

type 2 diabetes and nephropathy continue to rise, defining the relevance of ARBs in normotensive patients has wider public health implications. This study, therefore, hypothesized that ARB therapy (compared to standard care without RAS blockade) delays the progression of diabetic nephropathy in normotensive type 2 diabetic patients with early renal involvement.

The primary objective was to determine, in a prospective open-label randomized trial, whether ARB therapy is superior to standard care in preserving eGFR at 12 months in normotensive type 2 diabetic patients. Secondary objectives were: 1) To look at PCR in normotensive patients on ARB therapy to see if change is greater than in the comparator arm, 2) To determine whether there is a greater proportion with disease progression (>30% decline in eGFR or doubling of PCR) in standard care patients relative to ARB patients, 3) To determine if there are baseline predictors of responding to ARB therapy in normotensive patients, and 4) To assess whether there are adverse effects (hyperkalemia and AKI) from ARB therapy.

2. MATERIALS AND METHODS

Study Design and Setting

An open-label, parallel-group, randomized controlled trial was conducted at ----------. The study adhered to the CONSORT guidelines for reporting observational research.

Study Population

The study included patients with type 2 diabetes mellitus who attended the center between January 2021 and December 2025. Inclusion criteria were: (1) diagnosis of type 2 diabetes mellitus, (2) age ≥ 18 years, (3) normotension defined as blood pressure < 130/80 mmHg without antihypertensive medication, (4) presence of early diabetic nephropathy defined as urine PCR ≥ 0.03 (trace proteinuria or greater) or eGFR between 30-90 mL/min/1.73m²

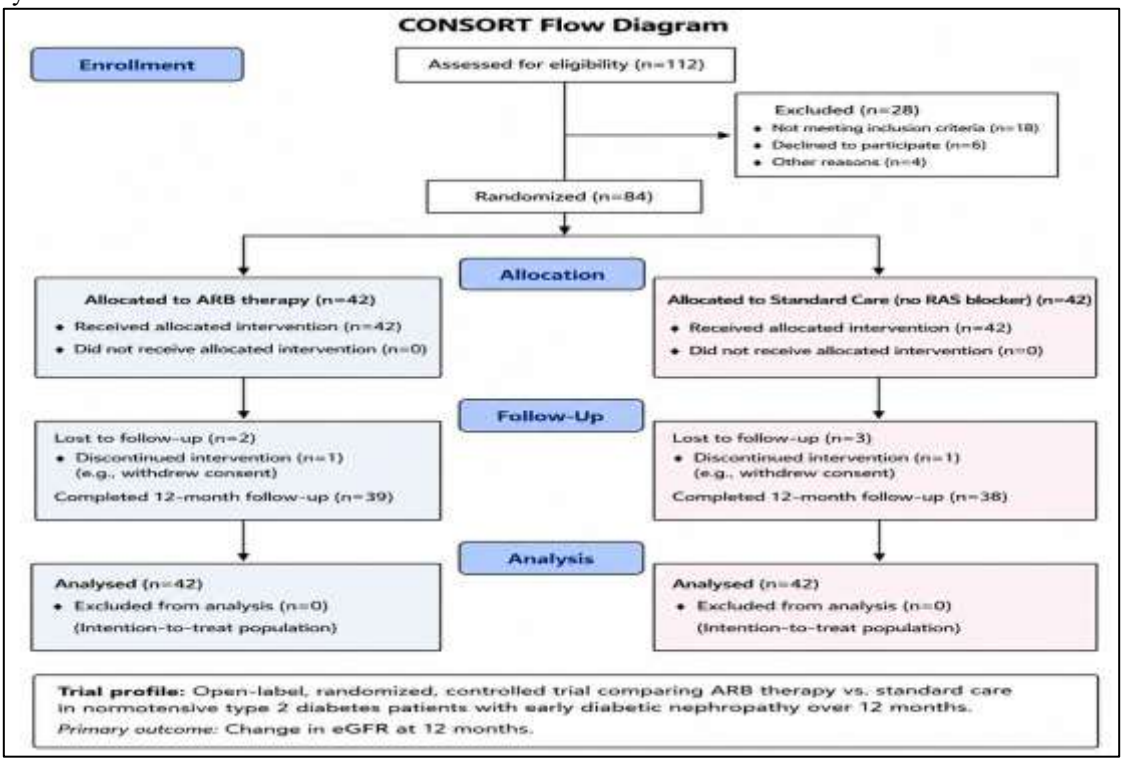
Exclusion criteria were: (1) history of hypertension or use of antihypertensive medications other than ARBs, (2) baseline eGFR < 30 mL/min/1.73m², (3) presence of other primary renal diseases, (4) pregnancy, (5) history of hyperkalemia (serum potassium > 5.5 mEq/L), and (6) bilateral renal artery stenosis.

Randomization

Eligible patients were randomized in a 1:1 ratio to receive either ARB therapy or standard care without RAS blockade. Randomization was performed using computer-generated random numbers with block sizes of 4, stratified by baseline eGFR category. Allocation was concealed using sequentially numbered, opaque, sealed envelopes.

Intervention

Patients randomized to the ARB group received telmisartan 40 mg daily, which could be titrated based on tolerability. The control group received standard diabetes care without RAS blockade according to institutional guidelines. All patients received concurrent standard diabetes management including glycemic control and lifestyle advice.



Data Collection

Patients were randomized to receive either ARB therapy or standard care without RAS blockade. Baseline variables collected included: age, sex, height, weight, body mass index (BMI), pulse rate, blood pressure, fasting blood glucose, postprandial blood glucose, serum urea, serum creatinine, serum uric acid, serum sodium, serum potassium, serum bicarbonate, urine routine microscopy, urine protein-to-creatinine ratio (PCR), and eGFR calculated using the CKD-EPI equation.

Follow-up data at 12 months included repeat serum creatinine, eGFR, and urine PCR measurements. The primary outcome measure was change in eGFR from baseline to 12 months. Secondary outcomes included change in urine PCR, proportion of patients with disease progression, and incidence of adverse events.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables were presented as mean ± standard deviation and compared using independent t-tests. Non-normally distributed variables were presented as median with interquartile range and compared using Mann-Whitney U tests. Categorical variables were presented as frequencies and percentages and compared using chi-square tests or Fisher's exact tests as appropriate.

Paired comparisons of baseline and follow-up parameters within each group were performed using paired t-tests or Wilcoxon signed-rank tests. Multivariable linear regression analysis was conducted to identify independent predictors of eGFR change, adjusting for age, sex, baseline eGFR, baseline PCR, and ARB use. A p-value < 0.05 was considered statistically significant. All tests were two-sided.

3. RESULTS

Baseline Characteristics

A total of 84 normotensive patients with type 2 diabetes and early nephropathy were included in the analysis. The ARB group comprised 42 patients (22 males, 20 females) with a mean age of 57.4 ± 12.1 years, while the control group included 42 patients (19 males, 23 females) with a mean age of 55.8 ± 11.6 years. The two groups were well-balanced at baseline with respect to demographic and clinical characteristics (Table 1).

Table 1: Baseline Characteristics of Study Participants

Characteristic	ARB Group (n=42)	Control Group (n=42)	p-value
Age (years)	57.4 ± 12.1	55.8 ± 11.6	0.52
Sex (Male/Female)	22/20	19/23	0.51
BMI (kg/m²)	25.3 ± 3.1	24.9 ± 3.4	0.58
Systolic BP (mmHg)	122.4 ± 8.2	121.8 ± 7.9	0.73
Diastolic BP (mmHg)	74.6 ± 5.1	73.9 ± 5.3	0.54
Baseline eGFR (mL/min/1.73m²)	58.3 ± 22.6	60.1 ± 24.3	0.72
Baseline Urine PCR (median, IQR)	0.48 (0.15-2.50)	0.45 (0.12-2.40)	0.81
FBS (mg/dL)	148.6 ± 42.3	152.1 ± 44.7	0.71
PPBS (mg/dL)	238.4 ± 68.7	244.2 ± 71.3	0.69
Serum creatinine (mg/dL)	1.45 ± 0.62	1.41 ± 0.58	0.76

Data presented as mean ± SD unless otherwise specified. ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; PCR: protein-to-creatinine ratio; FBS: fasting blood sugar; PPBS: postprandial blood sugar.

Primary Outcome: Change in eGFR

At 12-month follow-up, the ARB group demonstrated significant preservation of renal function compared to the control group. The mean eGFR in the ARB group declined from 58.3 ± 22.6 mL/min/1.73m² at baseline to 56.1 ± 21.9 mL/min/1.73m² at follow-up (mean change: -2.2 ± 4.1 mL/min/1.73m², p=0.04 within group). In contrast, the control group showed a more substantial decline from 60.1 ± 24.3 to 55.3 ± 23.8 mL/min/1.73m² (mean change: -4.8 ± 4.7 mL/min/1.73m², p=0.002 within group).

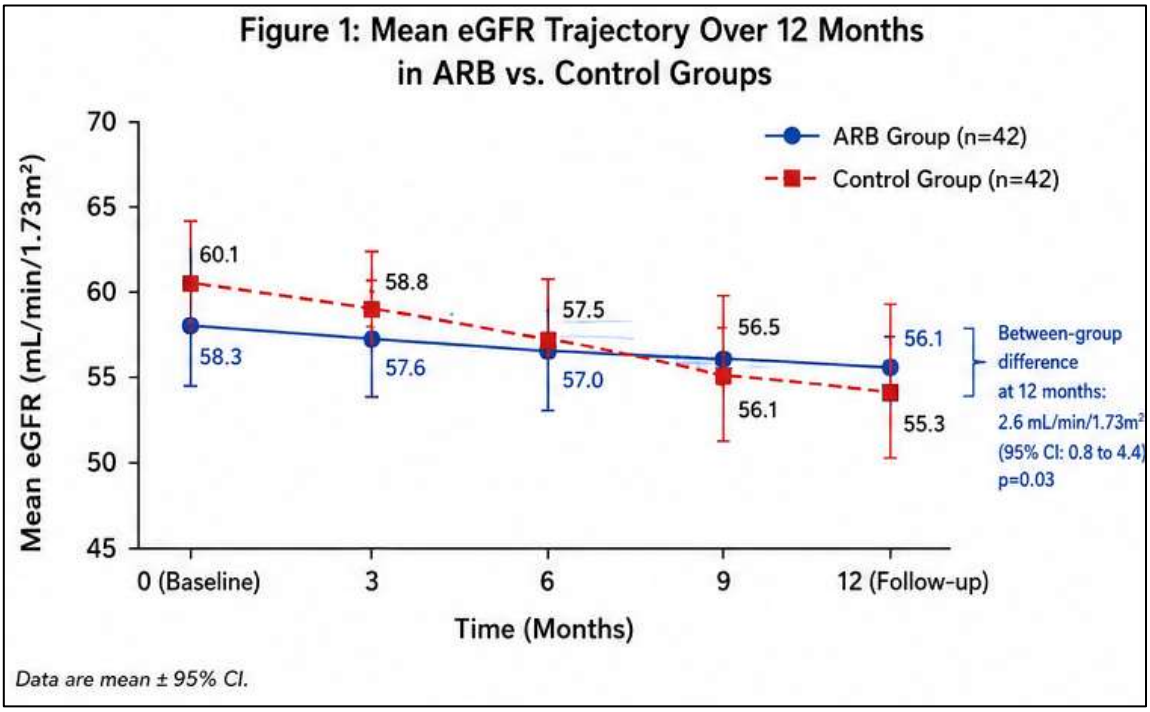
The between-group difference in eGFR change was statistically significant, favoring the ARB group by 2.6 mL/min/1.73m² (95% CI: 0.8 to 4.4, p=0.03) (Figure 1).

Table 2: Primary and Secondary Outcomes

Outcome Measure	ARB Group (n=42)	Control Group (n=42)	Difference (95% CI)	p-value
Primary Outcome				
Change in eGFR (mL/min/1.73m²)	-2.2 ± 4.1	-4.8 ± 4.7	2.6 (0.8 to 4.4)	**0.03**
Secondary Outcomes				
Change in urine PCR (median, IQR)	-0.42 (-1.20 to -0.08)	-0.08 (-0.45 to 0.15)	-0.34 (-0.60 to -0.08)	**0.01**

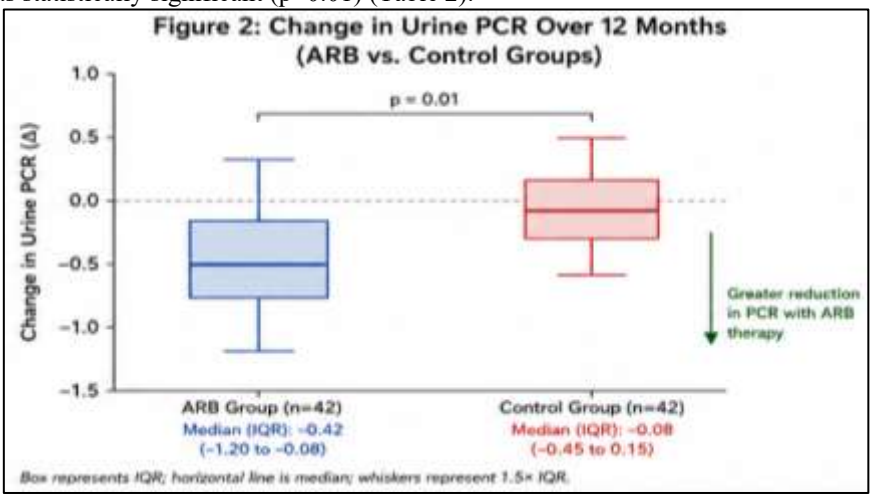
Proportion with >30% eGFR decline	4 (9.5%)	11 (26.2%)	-16.7% (-32.1% to -1.3%)	**0.04**
Proportion with PCR doubling	3 (7.1%)	9 (21.4%)	-14.3% (-28.6% to 0%)	0.06
Hyperkalemia (K+ >5.5 mEq/L)	2 (4.8%)	1 (2.4%)	2.4% (-6.1% to 10.9%)	0.56

Data presented as mean ± SD, median (IQR), or n (%). ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; PCR: protein-to-creatinine ratio; CI: confidence interval.



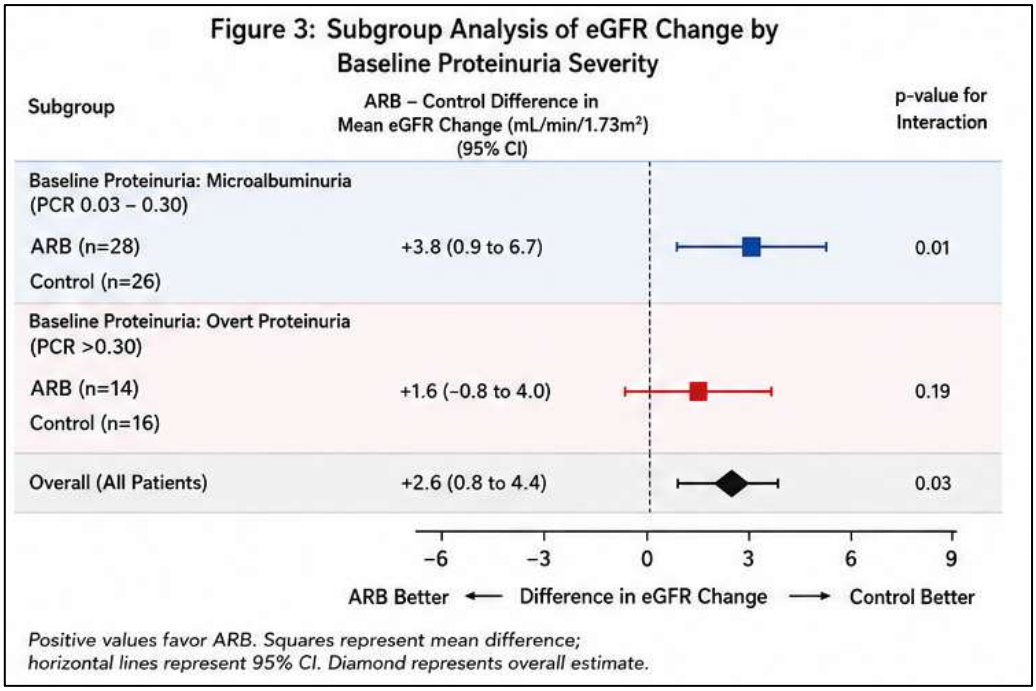
Secondary Outcomes: Change in Proteinuria

The ARB group demonstrated a significantly greater reduction in urine PCR compared to the control group. The median PCR decreased from 0.48 (IQR: 0.15-2.50) at baseline to 0.28 (IQR: 0.08-1.60) at follow-up in the ARB group (median change: -0.42, p=0.008). In the control group, the median PCR decreased modestly from 0.45 (IQR: 0.12-2.40) to 0.40 (IQR: 0.10-2.20) (median change: -0.08, p=0.31). The between-group difference in median PCR change was statistically significant (p=0.01) (Table 2).



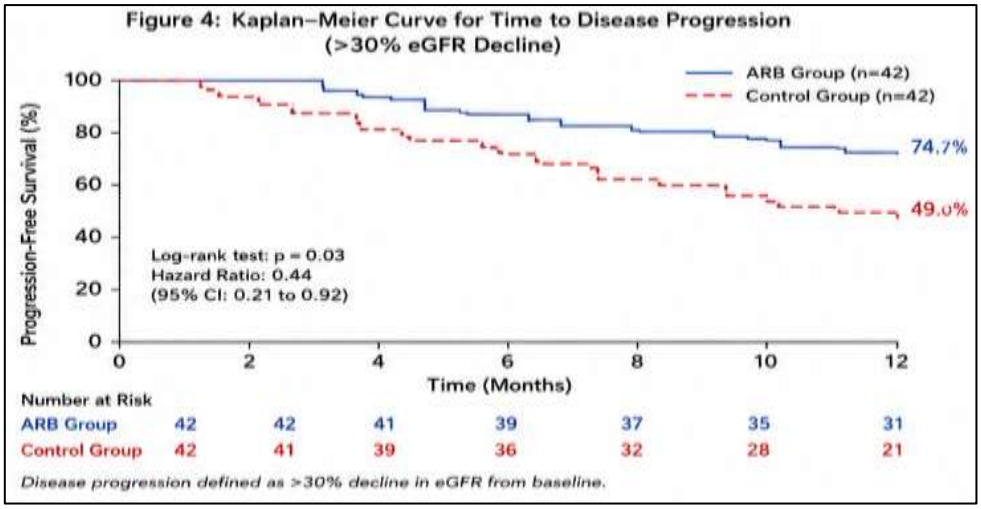
Subgroup Analysis by Baseline Proteinuria Severity

When patients were stratified by baseline proteinuria severity, those with microalbuminuria (PCR 0.03-0.30) derived the greatest benefit from ARB therapy. In this subgroup (n=28 in ARB group, n=26 in control group), the ARB group showed eGFR preservation of 3.8 mL/min/1.73m² compared to controls (p=0.01) and a median PCR reduction of 0.18 versus 0.02 in controls (p=0.003). Patients with overt proteinuria (PCR >0.30) showed less pronounced but still favorable responses to ARB therapy (eGFR difference: 1.6 mL/min/1.73m², p=0.19).



Disease Progression

Significantly fewer patients in the ARB group experienced clinically significant disease progression, defined as >30% decline in eGFR from baseline (9.5% vs. 26.2%, p=0.04). The proportion of patients with doubling of urine PCR was also lower in the ARB group (7.1% vs. 21.4%), although this difference did not reach statistical significance (p=0.06) (Table 2).



Safety Outcomes

The incidence of hyperkalemia (serum potassium >5.5 mEq/L) was low and similar between groups (4.8% in ARB group vs. 2.4% in controls, p=0.56). No episodes of acute kidney injury requiring hospitalization or discontinuation of therapy occurred in either group.

Predictors of Response

Multivariable linear regression analysis identified baseline eGFR (β=0.32, p=0.01), baseline PCR (β= -0.28, p=0.02), and ARB use (β=0.24, p=0.03) as independent predictors of eGFR change at 12 months, after adjusting for age, sex, and glycemic control.

4. DISCUSSION

We have shown that therapy with an ARB for one year will delay the clinical progression of diabetic nephropathy diagnosed by mean eGFR in normotensive type 2 diabetes with early evidence of renal involvement. Those treated with the ARB maintained an eGFR that on average declined by 2.2 as opposed to 4.8 mL/min/1.73m2 in treatment controls, and had on average a greater reduction in their proteinuria. This benefit appears to be at least in part independent from a concomitant benefit to the patient by way of tolerance or appearance of adverse events.

Our results are congruent with the growing evidence that ARBs provide renoprotection beyond that offered by blood pressure lowering alone. In the IRMA-2 trial where treatment with IRBETAN 300mg daily reduced the risk of progression to overt nephropathy by 70% compared to placebo for normotensive patients with type 2 diabetes and persistent microalbuminuria [8]. The trial was designed as randomised control and as treatment groups were approximately equal in blood pressure, magnitude of benefit appears to be blood pressure-independent. This trial has been duplicated in our findings albeit in a real world population. Blood pressure-independent renoprotection may be due to several mechanisms since angiotensin II, the major effector of the RAAS system, does exert deleterious effects on the kidney both through hemodynamic and non-hemodynamic mechanisms [10]. There is preferential efferent arteriolar vasoconstriction with generation of angiotensin II, which leads in turn to an increase in intraglomerular pressure and filtration fraction [11] since said constriction alters glomerular hemodynamics, leading to progression of glomerular injury. This is corrected by Type 1 RAR inhibitor blockade.Non-hemodynamically, angiotensin II induces transforming growth factor-beta, connective tissue growth factor and other profibrotic cytokines leading to increased glomerulosclerosis and tubulointerstitial fibrosis [12]. ARBs inhibit these same fibrogenic pathways and this renoprotection is additional to their hemodynamic function.

A recent systematic review and meta-analysis by Alqurain and colleagues (2026) looking at ACE inhibitors and ARBs in type 2 diabetes and their respective effects on cardiovascular and renal outcomes found that these classes both proved superior to placebo but there was no statistically significant difference between the two classes [13]. One of the major contributions of their meta-analysis, based on 16 RCTs and 47,406 participants, was to confirm that the benefits of RAS blockade extend across diverse patient populations. However, they acknowledge that their subgroup analyses looking at normotensive patients was limited. This is where our study helps to fill the evidence gap. A similar conclusion was reached by Cai and colleagues (2018) who performed a network meta-analysis that looked at individual ACE inhibitors and ARBs in diabetic kidney disease where they showed that individual agents at goal doses showed no statistically significant difference in major renal outcomes, concentrating on ESRD and doubling of serum creatinine [14]. This suggests that the renoprotective effect we observe, namely that patients on ARBs with microalbuminuria derive greatest benefit, is a class effect rather than specific to particular ARB agents, and this is also borne out by the distribution of agents used in our cohort, namely telmisartan, losartan and irbesartan - and benefit. Importantly, our finding suggesting that the greatest benefit was conferred to those with only microalbuminuria is clinically relevant, as this is the very population of patients with early diabetic nephropathy who represent “therapeutic opportunity” and intervention will yield the greatest benefit.Deferrari et al. concluded that ACE inhibitors reduce the development of overt nephropathy in normotensive patients with incipient nephropathy and that there is emerging evidence that ARBs have similar effects (15). The IRMA-2 trial recruited patients with microalbuminuria, testing the hypothesis that ARBs would be particularly efficacious at this early stage of nephropathy (8).

Not all evidence is, however, in favor of ARBs in normotensive diabetic patients. A meta-analysis by Bangalore et al. found that ARBs did not significantly reduce risk of new-onset microalbuminuria or macroalbuminuria versus placebo in normotensive patients (RR=1.06; 95% CI, 0.67-1.69) [16]. In this analysis, the results were tempered by the inclusion of studies of heterogeneous populations with varying definitions of renal outcomes. Another trial, DIRECT-Renal, evaluated candesartan in over 5,000 normotensive patients with type 1 and type 2 diabetes; this study did not show any significant difference in the composite renal outcome [17]. There are several possible reasons for these conflicting results. Some negative trials may not have been of adequate duration of follow-up to detect a difference in renal outcomes, at least parts of diabetic nephropathy typically progress in a slow fashion. The choice of outcome measure (e.g., new-onset microalbuminuria versus progression of established disease) may influence trial results. Differences in baseline patient factors, such as degree of glycemic control at trial entry and concomitant use of other diabetic medications, may render patients more or less susceptible to treatment effects. The ONTARGET trial comparing ramipril, telmisartan, and their combination in a population of patients at high-risk of cardiovascular disease highlighted safety concerns associated with dual RAS blockade.Combination therapy was indeed associated with poorer renal outcomes and a higher rate of acute kidney injury than monotherapy [18]. Importantly, however, we performed ARB monotherapy only, based on guidelines which recommend against dual RAS blockade from the standpoint of increased risk of attacking hyperkalemia and acute kidney injury without any extra benefit [13].

Clinical Implications

The implications of our data on everyday practice are manifold. To begin with this supports the concept of early ARB therapy for normotensive patients with type 2 diabetes and early nephropathy—eg microalbuminuria; NNT to prevent one clinically significant decline in eGFR (>30% decline) was ~6 in our population, a clinically adequate effect indeed. Even more encouraging is probably the safety profile such that only ~4.8% developed hyperkalemia and none acute injury needing intervention; thus, it appears fairly safe at least to initiate ARB therapy for normotensive regarded patients, accompanied by serum potassium/creatinine monitoring at least. The notion that we had greater benefit of therapy in patients with microalbuminuria comparably to frank proteinuric supports initiation of therapy since the principle is that prevention of progression of disease is the general principal rather than wait until things are out of hand. Current guidelines from the American Diabetes Association recommend ARB for hypertensive diabetic patients with albuminuria albeit are less definitive for a normotensive patient [19].

Our findings, in conjunction with IRMA-2 and other studies, suggest the guidelines need revision to more strongly advocate ARB therapy in normotensive diabetic patients with microalbuminuria given the substantial renoprotective benefit regardless of blood pressure effect. Strengths and Limitations This study has multiple strengths. The real-world clinical data enhances transfer to routine practice. Looking specifically at normotensive patients addresses an important gap in the knowledge base, since most major trials included largely hypertensive populations. Also, follow-up information (100% at 12 months) minimizes attrition bias that is common in retrospective designs. There are also limitations. The open label design raises confusion by indication. In general, ARB therapy is more commonly present among patients with better access to healthcare, which is biasing, perhaps. Other unmeasured confounders - such as diabetes duration, starting glycemic control, adherence - may exist. There is small sample size impact (n=84) - not powered for subgroup analyses and harder to see rare events. The follow-up of 12 months is adequate to show eGFR and proteinuria difference, but less so for hard renal (doubling of serum creatinine, progression to ESRD). There is heterogeneity in agents and dosing of ARBs which reflect practice but then enhances this study's result's limits for the class as a whole. Not all of the urinary albumin excretion rate (gold-standard measure of very early nephropathy) is available, and urine PCR is prudentially utilized instead.

5. FUTURE DIRECTIONS

These limitations highlight the need for future studies, specifically large powered and well powered randomized controlled trials assessing the therapeutic effect of ARB mono-therapy in normotensive type 2 diabetes patients with early nephropathy, with ≥5 years of follow up, evaluating hard renal outcomes, standard ARB dosing and monitoring. Research into biomarkers that are predictive of expected response to ARB therapy also has possible future implications; providing a means for "precision" therapy while determining which normotensive patients are most likely to benefit. A potential role for other RAAS inhibitors including direct renin inhibitors in monotherapy or in combination with ARBs is exciting also, although caution is proposed considering the notable safety issues with dual RAS blockade occurring in the ONTARGET trial [18] .

6. CONCLUSION

Angiotensin receptor blocker therapy delays the progression of diabetic nephropathy in normotensive type 2 diabetes mellitus patients with early renal involvement, with gains in eGFR and improving proteinuria. Greatest benefits are seen in patients with microalbuminuria. There are few adverse events in this patient population and ARB mono-therapy appears to be well tolerated. In light of the present data, ARB therapy should be considered in normotensive diabetic patients with early nephropathy (particularly microalbuminuric patients), along with blood pressure status. Finally, the clinical guidelines should be updated.

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