To cite this article: Melekoglu Ellik Z, Sayin B. Comparison of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker treatments of patients in 3 different patient groups with proteinuria. Turk J Clin Lab 2023; 3: 633-638

Research Article

Comparison of angiotensin converting enzyme inhibitor and/or angiotensin receptor blocker treatments of patients in 3 different patient groups with proteinuria

Proteinürisi olan 3 farklı hasta grubunda hastaların anjiotensin dönüştürücü enzim inhibitörü ve/veya anjiotensin reseptör blokörü tedavilerinin karşılaştırılması

Zeynep Melekoglu Ellik*[1], Burak Sayin[2]

[1]Karaman Training and Research Hospital, Department of Gastroenterology, Karaman, Turkey,
[2]Baskent University, Faculty of Medicine,Department of Nephrology and Transplantation, Ankara, Turkey.

Abstract

Aim: To evaluate the efficacy and safety of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for proteinuria in three different patient groups with chronic kidney disease (CKD).

Material and Methods:168 patients with diabetic nephropathy, glomerulonephritis, and renal transplantation who had more than 1 gram of daily urinary protein excretion were enrolled. The patients were divided into three groups: group 1 users of ACE inhibitors, group 2 users of ARBs, and group 3 users of both ACE inhibitors and ARBs. The clinical and laboratory parameters recorded for the patients included comorbid diseases, medications, blood urea nitrogen, creatinine, potassium, 24-hour urinary protein excretion, and creatinine clearance. Laboratory tests were recorded for months 0-1-3-6-9-12-18-24. Echocardiographic changes were recorded for months 0 and 24.

Results: In all three groups, a statistically significant decrease was observed between the proteinuria levels at month 0 and all other months. Patients receiving ACE inhibitors and ARBs had significantly higher creatinine levels after the 9th month. The patients in group 1 showed a significant decrease in creatinine clearance after the 9th month of the study. In contrast, patients in group 3 showed a significant decline after the 12th month of the study. In group 2, patients using ARBs showed no significant decrease in creatinine clearance.

Conclusion: Patients with proteinuria greater than 1g per day should receive ACE inhibitors or ARB treatment, and combined therapy of ACE inhibitors and ARBs should only be used in selected patients who can be closely monitored.

Keywords: Proteinuria, ACE inhibitors, ARB, RAAS inhibitors

Corresponding Author*: Zeynep Melekoglu Ellik, Karaman Training and Research Hospital, Department of Gastroenterology, Karaman, Turkey.
Orcid: 0000-0001-8290-7965
E-mail: zeynepmelekoglu33@hotmail.com
Doi: 10.18663/tjcl.1345274
Recevied: 17.07.2023 accepted: 27.09.2023

TJCL Volume 14 Number 3 p: 633-638

Öz

Amaç: Proteinürisi olan üç farklı hasta grubunda anjiyotensin dönüştürücü enzim (ACE) inhibitörleri ve anjiyotensin reseptör blokörlerinin etkinlik ve güvenliliğini değerlendirmek

Gereç ve Yöntemler: 24 saatlik idrarda 1 gramdan fazla proteinürisi olan diyabetik nefropati, glomerülonefrit ve böbrek transplantasyonu tanısı olan 168 hasta çalışmaya alındı. Hastalar 1. grup ACE inhibitörü kullananlar, 2. grup anjiyotensin reseptör blokörü (ARB) kullananlar ve 3. grup hem ACE inhibitörü hem de ARB kullananlar olarak üç gruba ayrıldı. Hastaların eşlik eden hastalıkları, kullandığı ilaçlar ve kan üre nitrojeni, kreatinin, potasyum, 24 saatlik idrar protein atılımı, kreatinin klirensini içeren laboratuvar değerleri 0-1-3-6-9-12-18-24.aylarda kaydedildi. Hastaların çalışma başlangıcı ve takibi sonunda ekokardiyografik değişiklikleri kaydedildi.

Bulgular: Her üç grupta da 0. aydaki proteinüri değerleri ile diğer tüm aylardaki proteinüri değerleri arasında istatistiksel olarak anlamlı bir düşüş gözlendi. Hem ACE inhibitörü hem de ARB'leri kullanan grup 3 hastalarda 9. aydan itibaren kreatinin seviyeleri anlamlı derecede yükseldi. Grup 1'deki ACE inhibitörü kullanan hastalarda takibin 9. ayından sonra kreatinin klirensi değerlerinde anlamlı bir azalma saptanırken, grup 3'teki ACE inhibitörü ve ARB kullanan hastaların 12. aydan sonra kreatinin klirensleri değerlerinde istatiksel olarak anlamlı bir düşüş saptandı. Grup 2'de ARB kullanan hastalarda kreatinin klirensinde anlamlı bir azalma görülmedi.

Sonuç: 24 saatlik idrarda 1 g'dan yüksek proteinürisi olan hastalar ACEi veya ARB tedavileri almalı ve ACE inhibitörü ve anjiotensin reseptör blokörlerinin kombine tedavisi ise sadece yakından izlenebilecek seçilmiş hastalarda kullanılmalıdır.

Anahtar kelimeler: Proteinüri, ACEi, ARB, RAAS inhibitörleri

Introduction

Chronic kidney disease (CKD) is characterized by a reduction in kidney function, indicated by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 or the presence of kidney damage markers, or both, for at least three months, regardless of the underlying etiology [1]. The global prevalence of CKD is estimated to range from 8% to 16% [2]. The renin-angiotensin-aldosterone system (RAAS) has been a critical therapeutic target for CKD patients with proteinuria [3-5]. Recent guidelines include using ACE inhibitors (ACEi) or angiotensin receptor blockers (ARB) as the first line of treatment. Recent studies have shown that inhibition of RAAS is effective in regulating blood pressure (BP), reducing proteinuria, decelerating the advancement of renal disease, and facilitating the prevention of cardiovascular disease (CVD) [4,6]. Reducing proteinuria may decrease the risk of disease progression.

This study aimed to evaluate proteinuria, renal function tests, GFR changes, and two-year follow-up results under ACEi and ARB treatment in different patient groups with proteinuria above 1g/day.

Material and Methods

A total of 162 patients with proteinuria of 1 g/day and above, diabetic nephropathy, glomerulonephritis, and kidney transplantation between 2009 and 2015 at the Ankara Baskent University Hospital Nephrology Department participated in the study. The 2-year data of the patients was evaluated. The study did not include patients using sirolimus due to its proteinuric effect in renal transplant recipients. Patients were divided into three groups: using ACE inhibitors (group 1), using ARB (group 2), and using ACE inhibitors and ARB (group 3). Each patient's demographic, clinical, and laboratory values were recorded retrospectively. Patients' age, gender, 0-1-3-6-9-12-18-24th months creatinine, creatinine clearance, potassium, proteinuria levels in 24-hour urine, drugs, echocardiography findings at 0 and 24 months, comorbidities, and proteinuria etiologies were recorded. The patient's 24-hour urine proteinuria was measured with the turbidimetric method. The local ethics committee approved the study.

Statistical analysis

The Statistical Package for Social Sciences version 15.0 software was used to evaluate the data. Descriptive statistical data are expressed as frequency, number, mean standard deviation, or median (min-max). The Kolmogorov-Smirnov test evaluated the distribution properties of the numeric variables. The independent-sample t-test was used for intergroup comparisons of numeric variables with a normal distribution, and Mann-Whitney's U test was used for variables without a normal distribution. Categorical data were evaluated using Fisher's Exact Test and the chi-square test. The evaluation was made with the "Monte Carlo Simulation Method" to include these frequencies in the analysis with the criteria where the

expected frequencies are less than 20%. The p <0.05 and p <0.01 values were considered statistically significant.

Results

The mean age of the patients in the study was 47.56 ± 14.37 years. Of the patients, 60.5% (n:98) were female. The patients' proteinuria was categorized based on the following etiologies: 19.1% diabetic nephropathy, 45.7% glomerulonephritis, and 35.2% renal transplant recipients. The prevalence of hypertension was 52.5%, diabetes mellitus was 32.7%, coronary artery disease was 16%, and cerebrovascular disease was 6.2% of patients. The clinical characteristics of the patients are shown in Table 1. When the causes of end-stage renal disease of the renal transplant recipients were evaluated in terms of etiology, 47% were glomerulonephritis, 21% were idiopathic, 18% were hypertension, and 14% were diabetic nephropathy.

Table 1. Clinical characteristics of the patients

		(n=162)	%
Gender	Female	98	60.5
	Male	64	39.5
Age	≤25	5	3.1
	>25 ve ≤45	75	46.3
	>45 ve ≤65	62	38.3
	>65	20	12.3
	Mean ± SD: 47.56 ± 14.37, Median: 46.0		
Other disease	Hypertension	85	52.5
	Coronary Artery Disease	26	16
	Diabetes Mellitus	53	32.7
	Previous Cerebrovascular Event	10	6.2
Proteinuria Etiology	Diabetic Nephropathy	31	19.1
	Glomerulonephritis	74	45.7
	Renal Transplantation	57	35.2

In this study, 34% of the patients (n:55) received ACE inhibitors, 36.4% (n:59) received ARBs, and 29.6% of the patients (n:48) were using both ACE inhibitors and ARBs concurrently (Table 2).

Table 2. The distribution of drug use among patients

Drug	Using		Not using		Total	
	n	%	n	%	n	%
ACEi	55	34	107	66	162	100
ARB	59	36.4	103	63.6	162	100
ACEi+ ARB	48	29.6	114	70.4	162	100
Corticosteroid	127	78.4	35	21.6	162	100
Cyclophosphamide	22	13.6	140	86.4	162	100
Cyclosporine	72	44.4	90	55.6	162	100
Azathioprine	9	5.6	153	94.4	162	100
Tacrolimus	37	22.8	125	77.2	162	100
Mycophenolate Mofetil	59	36.4	103	63.6	162	100
Beta Blocker	25	15.4	137	84.6	162	100
Calcium Channel Blocker	26	16	136	84	162	100

In all three groups, a statistically significant decrease was observed between the proteinuria levels at month 0 and the mean proteinuria levels at months 1, 3, 6, 9, 12, 18, and 24 (p <0.005). (Figure 1).

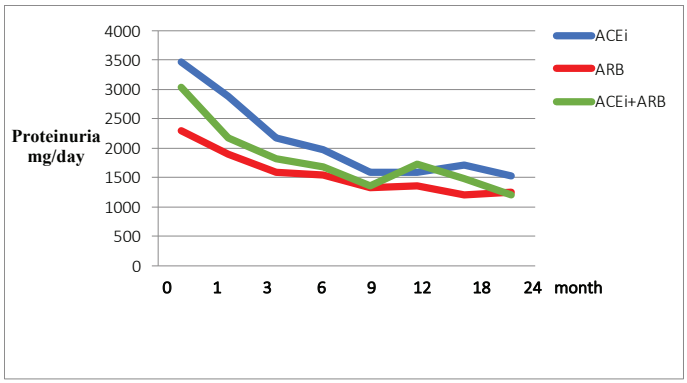

Figure 1. Change of proteinuria levels over time according to drug subgroups

When creatinine levels were evaluated in the groups, there was a statistically significant increase between the 0th and the 24th months of patients group 1 (p = 0.023). In addition, a statistically significant increase was observed in the mean creatinine levels at the 9th, 12th, and 18th months in group 3 using ACE inhibitors and ARBs. (p = 0,034, p = 0,049, p = 0,025) (Figure 2).

When the creatinine clearance of the groups was evaluated, a statistically significant decrease was observed between the creatinine clearance levels at month 0 and the mean creatinine clearance levels at months 9, 18, and 24 in group 1. (p=0.017, p=0.015, p=0.00). Also, in group 3, there was a statistically significant decrease between the creatinine clearance value at month 0 and the mean creatinine clearance value at months 12, 18, and 24. (p=0.025, p=0.015, and p=0.033). In group 2, patients using ARBs showed no significant decrease in creatinine clearance (Figure 3).

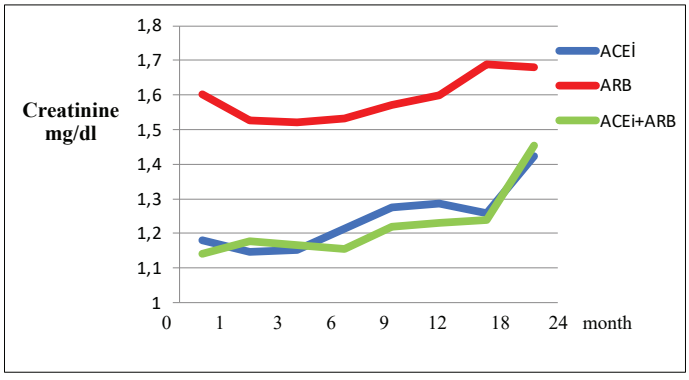

Figure 2. Change of creatinine levels over time according to drug use

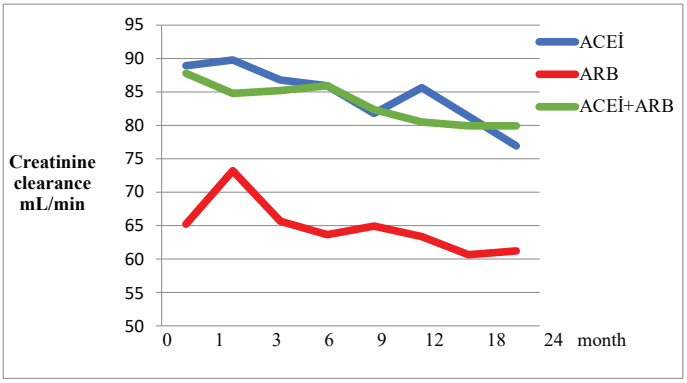

Figure 3. Change of creatinine clearance by drug groups over time

In addition, when the potassium levels were examined, a statistically significant decrease was observed in potassium levels between the 0th and 3rd months in only group 2 using ARBs (p = 0.043) (Figure 4).

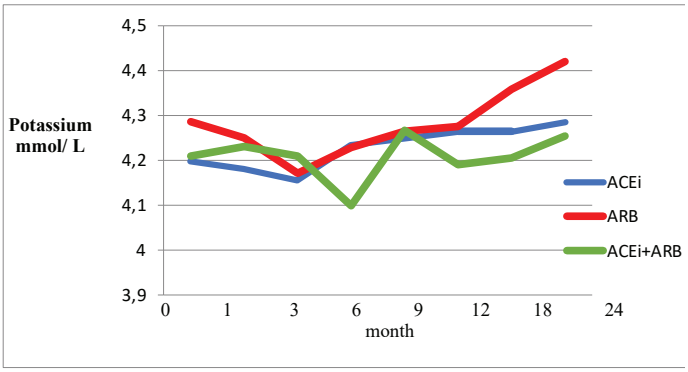

Figure 4. Change of potassium levels over time according to drug subgroups

Ejection fraction (EF) was evaluated by transthoracic echocardiography at the beginning and end of the two-year follow-up. There was no significant change in EF in the three groups. Also, there was no statistically significant difference between the groups when the groups were examined for left ventricular concentric hypertrophy (LVH) based on drug usage.

Discussion

In this study, a statistically significant decrease was observed between the proteinuria levels at month 0 and the mean control proteinuria levels in all other months in all three groups. It is known that there is a relationship between urinary protein excretion, treatment response, and progression of CKD in non-diabetic patients [7-9]. On the other hand, studies on proteinuria treatment and its effects in patients with type 2 diabetes are not sufficient [5,10]. It has been shown that antihypertensive treatments with RAS inhibitors provide more benefit than other treatments in patients with CKD with proteinuria [3]. While most of the studies in nondiabetic proteinuric patients were on ACE inhibitors, studies on the renoprotective effect of ARBs were mainly conducted on patients with diabetic nephropathy [12,13]. Although they have renoprotective effects similar to those of ACE inhibitors in nondiabetic CKD, supporting information is limited [11-13]. In this study, regardless of the primary disease, the decrease in proteinuria detected in the early period shows that ACE inhibitors and ARBs are beneficial in controlling proteinuria; combined use does not have an additive or synergistic effect. However, in selected patients with uncontrolled proteinuria with ACE inhibitors or ARBs alone, their concomitant use, even at the minimum dose, did not produce dangerous side effects. In the meta-analysis of randomized studies, there is evidence supporting the benefit of ACE inhibitors and ARBs in patients with proteinuria; the decrease in proteinuria is greater than that induced by other antihypertensive drugs. Although a meta-analysis showed that ARBs were more effective than ACEIs in reducing proteinuria in hypertensive patients, another recent meta-analysis found that treatment with ARBs and ACEIs had similar effectiveness in improving blood pressure and preventing progression of proteinuria/albuminuria. In the same way, the data we obtained in our study suggest that ARBs are at least as beneficial as ACE inhibitor treatments [14-17]. This study indicates that the treatment of ARBs is at least as beneficial as ACE inhibitors. This suggests that ARBs may be appropriate, especially in patients with severe side effects such as cough or angioedema that limit the use of ACE inhibitors.

In a meta-analysis of 1860 nondiabetic patients with CKD treated with a placebo or other antihypertensive medications, ACE inhibitors had a substantially lower progression rate of end-stage renal disease (ESRD) than other medications. RAAS blockade has an antiproteinuric effect even when the protein level mentioned in the discussion is below 1 g/day. However, its effects are more pronounced in patients with 1 g/day[18]. In our study, proteinuria levels are at least 1000 mg/day; it seems impossible to comment on the effects of ACE inhibitors and ARB use in patients with moderate proteinuria. On the other hand, at the end of the two-year follow-up, there was an increase in creatinine levels in patient group 1. This increase became statistically significant in the 9th month in the group 3. This can be interpreted as potentiating the adverse effects of both drug groups on renal function over each other. However, it should be emphasized that none of the patients developed ESRD, even in the combination group. Using an ACE in-

hibitor with an ARB, one of which is the minimal dosage, could treat persistent proteinuria. A meta-analysis of 12 studies of proteinuric patients with severe or moderately severe albuminuria confirmed that ACE inhibitors and ARBs reduce CKD progression. The incidence of ESRD is lower in treatments with ACE inhibitors and ARB treatments [19]. The 2-year follow-up period in this study may be why we did not see any patients progressing to ESRD. A 5-year follow-up of the same patient groups will provide a more appropriate interpretation of the effects on renal and patient survival.

The creatinine clearance levels of patients in group 1 decreased significantly from the 9th month, while those in group 3 receiving combined drug therapy were statistically significant from the 12th month. Group 2 patients saw no significant decrease in creatinine clearance. The study showed that GFR levels could only be maintained in group 2, even though the decline in creatinine clearance is a normal consequence of the CKD course. However, proteinuria control was achieved in all three groups.

When the patients' potassium levels were analyzed, a statistically significant decrease was observed between the patient's potassium levels in group 2 at the 0th month and the 3rd month ($p=0.04$). The fact that the patients were warned about potassium-containing foods and drinks and were followed very closely may explain the successful results in hyperkalemia. However, due to the many negative examples in the literature, patients who can be followed closely and follow a potassium-restricted diet without exception should be preferred for the combined use of ACE inhibitors and ARBs [20].

Comparing the groups for LVH according to treatment revealed no statistically significant differences. When the patients were grouped according to the diagnoses, there was no significant difference between the groups. It is known that both ACE inhibitors and ARBs have positive effects on cardiac remodeling [21,22]. Although our study did not demonstrate a significant positive impact on EF and LVH, the deterioration of cardiac functions can be prevented. We decide that the control of albuminuria, which has been independently proven to have adverse effects on cardiac functions, is the primary determinant of this condition.

In our study, no side effects were observed that could lead to the discontinuation of the treatment or exclusion of the patients from the study. This can be interpreted as the fact that most of the chronic kidney disease stages of the selected and included patients were at stage 3, and the risk of hyperkalemia was relatively low. Again, the follow-up period is limited to 2 years, which may be sufficient for the emergence of positive effects on proteinuria but insufficient for the evaluation of all kidney functions. Inadequate duration also applies to possible positive cardiac effects.

Conclusion

In conclusion, patients with proteinuria above 1g/day should initiate ACE inhibitor or ARB therapy, regardless of the underlying disease. In patients with uncontrolled proteinuria, concomitant administration of ACE inhibitors and ARBs may be safe only in a select group of compliant, closely monitored patients. Even though the use of ACE inhibitors and/or ARBs negatively affects renal function, 2-year follow-up results indicate that this negative impact does not lead to the progression of end-stage renal disease in patients.

Acknowledgments

No funding was secured for this study.

The authors have no financial relationships relevant to this article to disclose.

The authors declare no conflicts of interest to disclose.

The corresponding author's data supporting this study's findings are available upon reasonable request.

The study was approved by the ethics committee of Baskent University Medical Faculty (Date: 09/07/2015, Approval number: KA15/234).

Authors' contributions to the article

Conception and design of the study: ZME, CBS

Generation, collection, assembly, analysis, and/or interpretation of data; ZME, CBS

Drafting or revision of the manuscript; ZME, CBS

Approval of the final version of the manuscript; ZME, CBS

References

1. A. C. Webster, E. V. Nagler, R. L. Morton, and P. Masson, "Chronic Kidney Disease," Lancet, vol. 389, no. 10075, pp. 1238–1252, Mar. 2017, doi: 10.1016/S0140-6736(16)32064-5.
2. V. Jha et al., "Chronic kidney disease: global dimension and perspectives," Lancet, vol. 382, no. 9888, pp. 260–272, Jul. 2013, doi: 10.1016/S0140-6736(13)60687-X.
3. A. S. Levey and J. Coresh, "Chronic kidney disease," Lancet, vol. 379, no. 9811, pp. 165–180, Jan. 2012, doi: 10.1016/S0140-6736(11)60178-5.
4. R. Fagard, "Reappraisal of the European guidelines on hypertension management: the European Society of Hypertension Task Force document: a short review.," Pol. Arch. Med. Wewn., vol. 120, no. 1–2, pp. 31–5, 2010.

5. B. M. Brenner et al., "Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy," N. Engl. J. Med., vol. 345, no. 12, pp. 861–869, Sep. 2001, doi: 10.1056/NEJMoa011161.
6. D. S. Wald, M. Law, J. K. Morris, J. P. Bestwick, and N. J. Wald, "Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 Participants from 42 Trials," Am. J. Med., vol. 122, no. 3, pp. 290–300, Mar. 2009, doi: 10.1016/j.amjmed.2008.09.038.
7. T. H. Jafar et al., "Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis.," Ann. Intern. Med., vol. 139, no. 4, pp. 244–52, Aug. 2003, doi: 10.7326/0003-4819-139-4-200308190-00006.
8. J. Lea, "The Relationship Between Magnitude of Proteinuria Reduction and Risk of End-stage Renal Disease," Arch. Intern. Med., vol. 165, no. 8, p. 947, Apr. 2005, doi: 10.1001/archinte.165.8.947.
9. P. Ruggenenti, A. Perna, G. Gherardi, F. Gaspari, R. Benini, and G. Remuzzi, "Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial," Lancet, vol. 352, no. 9136, pp. 1252–1256, Oct. 1998, doi: 10.1016/S0140-6736(98)04433-X.
10. T. H. Hostetter, "Prevention of End-Stage Renal Disease Due to Type 2 Diabetes," N. Engl. J. Med., vol. 345, no. 12, pp. 910–912, Sep. 2001, doi: 10.1056/NEJM200109203451209.
11. P. A. Sarafidis, N. Khosla, and G. L. Bakris, "Antihypertensive Therapy in the Presence of Proteinuria," Am. J. Kidney Dis., vol. 49, no. 1, pp. 12–26, Jan. 2007, doi: 10.1053/j.ajkd.2006.10.014.
12. P. A. Sarafidis and G. L. Bakris, "Microalbuminuria and chronic kidney disease as risk factors for cardiovascular disease," Nephrol. Dial. Transplant., vol. 21, no. 9, pp. 2366–2374, Sep. 2006, doi: 10.1093/ndt/gfl309.
13. P. K.-T. Li et al., "Hong Kong Study Using Valsartan in IgA Nephropathy (HKVIN): A Double-Blind, Randomized, Placebo-Controlled Study," Am. J. Kidney Dis., vol. 47, no. 5, pp. 751–760, May 2006, doi: 10.1053/j.ajkd.2006.01.017.
14. J. P. Casas et al., "Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis," Lancet, vol. 366, no. 9502, pp. 2026–2033, Dec. 2005, doi: 10.1016/S0140-6736(05)67814-2.
15. I. Giatras, "Effect of Angiotensin-Converting Enzyme Inhibitors on the Progression of Nondiabetic Renal Disease," Ann. Intern. Med., vol. 127, no. 5, p. 337, Sep. 1997, doi: 10.7326/0003-4819-127-5-199709010-00001.
16. R. Xu et al., "Effects of ACEIs Versus ARBs on Proteinuria or Albuminuria in Primary Hypertension: A Meta-Analysis of Randomized Trials.," Medicine (Baltimore)., vol. 94, no. 39, p. e1560, Sep. 2015, doi: 10.1097/MD.0000000000001560.
17. Li CJ, Bu PL. Meta-analysis of efficacy of ACEI and ARB in treatment of proteinuria in essential hypertension. Med Recapitulate 2012; 17:2872–2884
18. T. H. Jafar, "Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease," Ann. Intern. Med., vol. 135, no. 2, p. 73, Jul. 2001, doi: 10.7326/0003-4819-135-2-200107170-00007.
19. A. Maione et al., "Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials," Nephrol. Dial. Transplant., vol. 26, no. 9, pp. 2827–2847, Sep. 2011, doi: 10.1093/ndt/gfq792.
20. A. V Chobanian et al., "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.," JAMA, vol. 289, no. 19, pp. 2560–72, May 2003, doi: 10.1001/jama.289.19.2560.
21. J. F. E. Mann et al., "Dual inhibition of the renin–angiotensin system in high-risk diabetes and risk for stroke and other outcomes," J. Hypertens., vol. 31, no. 2, pp. 414–421, Feb. 2013, doi: 10.1097/HJH.0b013e32835bf7b0.
22. B. Pitt et al., "Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomized trial—the Losartan Heart Failure Survival Study ELITE II," Lancet, vol. 355, no. 9215, pp. 1582–1587, May 2000, doi: 10.1016/S0140-6736(00)02213-3.