CSCanada
Advances in Natural Science
Vol. 7, No. 1, 2014, pp. 12-17
DOI:10.3968/4349

ISSN 1715-7862 [PRINT]
ISSN 1715-7870 [ONLINE]
www.cscanada.net
www.cscanada.org

Potential Reno-Protective Effects of Telmisartan in Kurd Non-Diabetic Hypertensive Patients in Hawler City

A. I. Muslih[a],*.

[a]College of Pharmacy, Hawler Medical University, Iraq.
*Corresponding author.

Received 23 November 2013; accepted 16 February 2014
Published online 27 March 2014

Abstract

Angiotensin II (AII) type I (AT1) receptor blockers are a well known group of drug that indicated principally for the treatment of hypertension as well as for the protection of kidney function in diabetic patients. Telmisartan is a highly selective angiotensin receptor blocker, and the favourable tolerability profile of telmisartan combined with its long elimination half- life ensure the drug provides pronounced reductions in blood pressure (BP) across the entire 24-hour dosage interval. There is relatively very little data and information available to reveal renoprotective activity of telmisartan in nondiabetic low grade albuminuric Kurd hypertensive patients. Our study explores the effect of telmisartan on mean arterial blood pressure and it also sheds more light on its crucial role in lowering albumin: creatinine ratio in Kurd patients. The results of our study demonstrate that telmisartan reduces mean arterial blood pressure significantly, furthermore the study had explained a significant reduction in albuminuria at the second month of treatment which is regarded as a positive sign of renoprotection.

Key words: ARBs; Albuminuria; Creatinine; Hypertension; Kurd race; Renal protection; Telmisartan

Muslih, A. I. (2014). Potential Reno-Protective Effects of Telmisartan in Kurd Non-Diabetic Hypertensive Patients in Hawler City. *Advances in Natural Science*, *7*(1), 12-17. Available from: http://www.cscanada.net/index.php/ans/article/view/4349
DOI: http://dx.doi.org/10.3968/4349

INTRODUCTION

Albuminuria (proteinuria) is well established to be a sensitive indicator of kidney disease (Yee et al., 2011), and its test is a powerful tool to screen individuals with chronic conditions such as hypertension and diabetes who are at high risk for renal damage (Özyilmaz, Bakker, de Zeeuw, de Jong, & Gansevoort, 2010), which means that the kidneys are not capable to retain or reabsorb filtered proteins back to the blood stream (Nordquist, Brown, Fasching, Persson, & Palm, 2009). Albuminuria most often occurs either when the glomerulus and/or renal microtubules are damaged (Satchell & Breat, 2009).

Increasing amounts of the albumin in urine is the reflection of more advanced renal failure (Ruilope & Bakris, 2011).

Creatinine a by-product of body metabolism is ordinarily excreted into the urine at a constant rate. Its measurement is used as a dependable factor in random urine samples (Brault & Terjung, 2003). Multi scientific centres have stated a preference for the microalbuminuria/creatinine ratio (ACR) calculation for screening for albuminuria (Sarafidis et al., 2007). Protein:creatinine ratio in spot morning urine samples is a precise indicator of proteinuria and a reliable predictor of disease in non-diabetic patients with chronic nephropathies (Guy, Borzomato, Newall, Kalra, & Price, 2009).

Reduction in both proteinuria and the rate of decline of glomerular filtration rate in chronic renal non diabetic diseases is mainly targeted by pharmacological blockade of the rennin-angiotensin-aldosterone system (RAAS) a principal therapy (Lizakowski et al., 2012; Muslih, 2012). In the chronic kidney disease (CKD) the presence of vascular dysfunction is documented (Loriga, Carru, Zinellu, Milia, & Satta, 2011). The presence of indistinctive risk factors such as proteinuria and vascular dysfunction, contribute to the excess of cardiovascular events (CVE) that characterizes chronic proteinuric nephropathy (Hirsch, 2008). Angiotensin II is a naturally occurring hormone that constricts blood and produces higher blood pressure (Redding et al., 2010). Insufficient suppression of RAAS involved in

the development of higher arterial pressure (Rahmoni, Correia, Haynes, & Mark, 2005). Prolonged course of treatment with several angiotensin converting enzyme inhibitors (ACEIs) has been shown to decrease the risk of renal disease in diabetic patients (Iqbal & Shah, 2011). As well the use of angiotensin receptor blockers (ARBs) has beneficial effects on renal function (Hunt et al., 2009). Patients unable to tolerate ACEIs because of angioedema and cough (Kloth & Lane, 2011), the newer class of antihypertensive medication ARBs have shown advantage by minimizing hospital admissions and mortality (Powers et al., 2012). Compared with lisinopril, telmisartan is associated with a significant lower incidence of persistent, dry cough (Sharpe, Jarvis, & Goa, 2001). ARBs have a benefit parallel to that of ACEIs during treatment of patients complain from left ventricular dysfunction (Savelieva, Kakouros, Kourliouros, & Camm, 2011) posterior to myocardial infarction (MI). Telmisartan has a unique profile among ARBs, with a high lipophilicity (Burnier & Maillard, 2009), a long duration of receptor binding conferring 24-hour coverage of blood pressure (BP) control from a single daily dose (Song & White, 2001), a high affinity for the angiotensin II type 1 receptor (Kakuta, Sudoh, Sasmata, & Yamagishi, 2005) and a long plasma half life (Zheng, Lin, & Shi, 2010). Many studies show that telmisartan is more effective than sub maximal dosages of losartan and valsartan (Fogari et al., 2012). An important characteristic feature is that telmisartan (amongst other ARBs) is a partial PPARγ agonist, a nuclear transcription factor that plays a role in the regulation of glucose and lipid metabolism, with this effect being independent of the BP lowering effects induced by AT1 antagonism (Yamagishi, Motsui, & Nakamura, 2008).

In spite of growing number of studies concerning pharmacological profile of ARBs, we find limited information about the renoprotective effect in patients with impaired renal function in nondiabetic hypertensive patients.

The aim of the study is to answer the following question: Does ARB (telmisartan) treatment exert renoprotective effects in addition to and at least in part independent of blood pressure reducing? To address the question, treatment was initiated in Kurd nondiabetic hypertensive patients and followed up over 6 months of treatment.

1. MATERIALS AND METHODS

Subjects were recruited from Kurd patients with hypertension, 25 years or older, who visited the Educational Rizgary Hospital/Hawler between January 2009 to July 2009 and with the participation of 47 patients afflicted with hypertension and on the basis of inclusion and exclusion criteria of the project (inclusion criteria: propensity to cooperation, affliction with hypertension, and exclusion criteria: patients have no other chronic disease and/or they are put on medicaments other than telmisartan. All the patients were informed of the aim of the study, and the potential effects of the procedure. The study was approved by the ethics committee of the Educational Rizgary Hospital/Department of Internal Medicine, and the study was conducted in accordance with the Declaration of Helsinki. All the patients signed a consent form approved by the ethics committee before the operation. Patients were allocated to receive telmisartan 80 mg/day, serum creatinine was measured before treatment and after 10 days to detect the difference between the two readings which was found to be less than 20%-30% over baseline value to all patients, based on this we can rule out any potentiality of precipitation of unilateral/bilateral artery stenosis (Hackam, Spence, Garg, Textor, 2007; Cianci, Martina, Borghesi, di Donato, Polidori, Lai, Ascoli, de Francesco, Zaccaria, Gigante, Barbano, 2011).

ACR was determined from a single morning urine sample that each patient delivered to the laboratory, and used to categorize subjects as follows: normoalbuminuria (ACR<30 mg/g), microalbuminuria (ACR<30-299 mg/g), macroalbuminuria (ACR>300 mg/g) (American Diabetes Association, 2004; Krimholtz, Karalliedde, Thomas, Bilous, Viberti, 2005). Glucose or contamination with bacteria does not affect the estimation of albumin. For each patient albuminuria was divided by urine creatinine to obtain the ACR which is expressed as mg/g, as follow:

$$\frac{\text{Urine albu min(mg/dl)}}{\text{Urine creatinine(g/dl)}} = ACR\ (\text{mg/g}) \qquad (1)$$

The urine albumin concentration was measured using a competitive immunoassay (Immulite®, DPC, Los Angeles, CA, USA). Urinary creatinine level was analyzed by the Jaffe reaction using the kits available inside the country.

1.1 Parameters Measured

Blood pressure was detected by two measurements in the sitting position after 5 minutes of taking rest, applying Korotkoff and Riva-Rocci technique (Brien, 2008; Shimizu & Kario, 2008). All the measurements were made by the same investigators on the patients dominant arm at 8:00 am: 11:00 am, mean arterial pressure was calculated according to:

$$\frac{\text{(Systolic pressure+2)*Diastolic pressure}}{3} \qquad (2)$$

1.2 Statistical Analysis

Results presented as mean+SEM. Paired Students *t*-test was used to analyze differences in variables before and after treatment. Comparison between different groups was conducted using one-way ANOVA followed by a Student-Newman-Keuls method. *P*-values<0.05 were considered statistically significant. The study data were analyzed by use of SPSS statistical software version 18.

2. RESULTS

Study results as in Table 1 includes two parts:

a. The figures demonstrate effects of telmisartan 80mg on albumin:creatinine ratio in non diabetic essential hypertensive patients. The level of ACR significantly decreased starting from the second month of the starting of the treatment compared to baseline time, while it is significantly decreased to below the normal range after 6 months of treatment. ACR decreased from 84±12.2 to 28.4±3.8 (p<0.05).

b. Reduction effect of telmisartan 80mg on blood pressure. Mean arterial pressure significantly (MAP) decreased after 1 month of treatment compared to baseline time. While treatment for 6 months significantly decreased MAP to below the normal blood pressure level, MAP decreased from 146±3.1mmHg to 101±1.1 mmHg (p<0.05).

Table 1
Decreasing Effects of Telmisartan 80mg on Albuminuria and Mean Arterial Pressure in Patients With Kurd Non-Diabetic Hypertensive Patients

Time (month)	Albumine: creatinine ratio (ACR) mg/g		Mean Arterial Pressure (MAP) mmHg	
	mean	SEM	mean	SEM
Baseline	84	12.2	146	3.1
1	80	11.3	134*	2.9
2	73.3*	9.1	125*	2
3	61.5*	7.3	118*	1.7
4	47.1*	6.4	111*	1.5
5	38.7*	5.2	107*	1.2
6	28.4*.	3.8	101*	1.1

Note. Values are mean±SEM; n=47. P<0.05

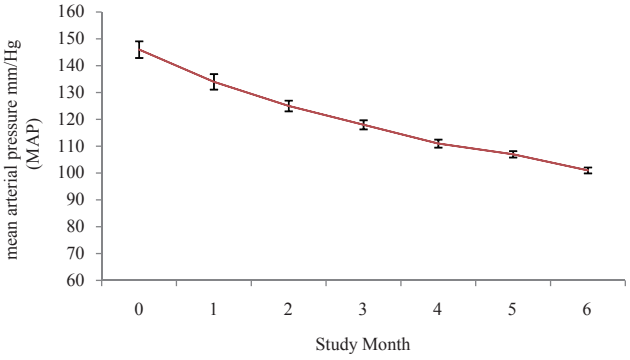

Figure 1
Impact of Telmisartan 80 mg-Based Regimen on the Rate of Reduction in Mean Arterial Pressure in Kurd Non-Diabetic Hypertensive Patients

3. DISCUSSION

The overwhelming body of evidence has shown that effective control of blood pressure (BP) reduces cardiovascular (CV) and renal risk in patients afflicted with hypertension (Mancia & Corrao, 2009). There are several mechanisms whereby activation of the RAS has been shown to play a role in the pathogenesis of renal disease (Rao, 2011). As the inhibition of Renin angiotensin system (RAS) has reducing effect on BP, it also in a different situation and according to recent studies exerts a renoprotective effect through reducing proteinuria.Increasing evidence indicates that the inhibition of RAS may exert a renoprotective effect that is independent of its effect on blood pressure reduction (Beri, 2009). RAS blockers [angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)] are well recognized, effective antihypertensive agents that exert their BP lowering effect through diverse pathways at various levels of the RAS (Verdecchia, Gentile, Angeli, & Reboldi, 2012). In the past two decades RAS inhibitors have become a building block for the treatment of hypertension. Angioneurotic odema and cough are amongst the most occurrence side effects associated with ACEIs, but in present study we did not find such association of cough and telmisartan. Furthermore inhibitors of RAS have been used in a wide manner in patients with renal disease as it is reported that the agents have antiproteinuric effect that is independent of the blood pressure lowering action (Bianchi et al., 2006) in another words RAS blockers that reduce BP, also reduce both proteinuria and do lessen glomerular filtration rate in chronic renal non diabetic diseases. Also it is observed by many researchers that proteinuria reducing therapies (ACEIs & ARBs) delay progression to diabetes (Akbari et al., 2009). Analytical data from clinical studies identify that ARBs may be more effective than other ACEIs or β blockers in stroke prevention. ARBs in contrast to ACEIs which do not produce dry cough, are increasingly used as antihyperternsive agents (White, Lacourciere, & Davidai, 2004).

The albumin to creatinine ratio (ACR) in a single untimed urinary specimen is a reflection of urinary albumin excretion and is increasingly being accepted as a marker that predicts several important health outcomes, including hypertension, kidney failure, cardiovascular events and mortality (Masson et al., 2010). Published data have shown that calculation of an albumin/creatinine ratio (ACR) in a spot urine sample has reasonable rate of sensitivity and specificity (Tuncel et al., 2004).

People who have consistently detectable amounts of albumin in their urine (microalbuminuria) have an increased risk of developing a progressive kidney failure and cardiovascular in the future. The presence of albumin in the urine (albuminuria) has been shown to be a sensitive indicator of kidney disease in patients with diabetes and with hypertension.

High systemic blood pressure leads to increased intraglomerular pressure, which in turn brings about mesangial cell hypertrophy and extracellular matrix

production, thickening of basement membrane and production of growth factor (Russo et al., 2008). Therefore, decrement of BP is necessary to prevent progression of renal abnormalities (American Diabetes Association, 2007; Mancia et al., 2011), accordingly, reduction in BP is observed as subsidiary factor that prevent pregression of renal abnormalities The present study confirms the antiproteinuric performance of antihypertensive drug telmisartan and provides an impressive and well-tolerated remedy of hypertension with significantly less likely to account for persistent dry cough than other ACEIs in patients with essential hypertension. The reduction in ACR level appeared clearly on Kurd patients after 2 and 3 months, a conclusion that is close to the results of many researchers (Ninomiy et al., 2009). The mechanisms mentioned above could be regarded as pathways demonstrating antialbuminuric effects of the drug. The results also shows efficacy of telmisartan to decrease significantly mean arterial pressure, a result which agree with other studies performed by many co-workers (Tobe et al., 2011).

ACKNOWLEDGMENT

We are thankful to Dr Ismail M. Mawlood of the Department of Biology, College of Science, Salahaddin University/ Hawler-Iraq, for his important and critical revision of the statistical analysis part manuscript.

ABBREVIATIONS AND ACRONYMS

ACEIs: angiotensin converting enzyme inhibitors; ACR: albumin: creatinine ratio; ARBs: angiotensin receptor blockers; AT1: angiotensin II type 1 receptor; BP: blood pressure; CKD: chronic kidney disease; CVE: cardiovascular events; ESRD: end-stage renal; disease; MAP: mean arterial pressure; MI: myocardial infarction; RAAS: renin-angiotensin-aldosterone system; RAS: renin-angiotesnsin system

REFERENCES

Akbari, A., Knoll, G., Ferguson, D., McCormic, K. B., Davis, A., & Biyani, M. (2009). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in peritoneal dialysis: Systematic reviewand meta-analysis of randomized controlled trials. *Perit. Dial. Int. 29*, 554-561.

American Diabetes Association. (2004). Nephropathy in diabetes. *Diabetes Care, 27* (Suppl. 1), S79–S83

American Diabetes Association. (2007). Standards of medical care in diabetes. *Diabetes Care, 30* (Suppl. 1), S19-S21.

Beri, T. (2009). Review: Renal protection by inhibition of the renin-angiotensin-aldosterone system. *Journal of Renin-Angiotensin-Aldosterone System*, *10*, 1. doi: 10.1177/1470320309102747

Bianchi, S., Bigazzi, R.. & Campese, V. M. (2006). Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int*, *70*, 2116-2123.

Brault, J. J., & Terjung, R. L. (2003). Creatine uptake and creatine transporter expression among rat skeletal muscle fiber types. *Am J Physiol Cell Physiol*, *284*, 1481-1489. doi: 10.1152/ajpcell.00484.2002

Burnier, M., & Maillard, M. (2009). The comparative pharmacology of angiotensin II receptor antagonists. *Blood Press Suppl*, *10*, 6-10. doi:10.1093/eurheartj/sup029.

Cianci, R., Martina, P., Borghesi, F., di Donato, D., Polidori, L., Lai, S., ... Barbano, B. (2011). Revascularization versus medical therapy for renal artery stenosis: Antihypertensive drugs and renal outcome. *Angiology*, *62*, 92-99. doi: 10.1177/0003319710371615

Fogari, R., Mugellini, A., Zoppi, A., Preti, P., Destro, M., Lazzari, P., & Derosa, G. (2012). Effect of telmisartan and ramipril on atrial fibrillation recurrence and severity in hypertensive patients with metabolic syndrome and recurrent symptomatic paroxysmal and persistent atrial fibrillation. *Journal of Cardiovascular Pharmacology and Therapeutics*, *17*, 34-43. doi: 10.1177/1074248410395018

Galle, J., Schwedhelm, E., Pinnetti, S., Böger, R. H., & Wanner, C., & on behalf of the VIVALDI investigators (2008). Antiproteinuric effects of angiotensin receptor blockers: telmisartan versus valsartan in hypertensive patients with type 2 diabetes mellitus and overt nephropathy Nephrol. *Dial. Transplant. 23*, 3174-3183. doi: 10.1093/ndt/gfn230

Guy, M., Borzomato, J. K., Newall, R. G., Kalra, P. A., & Price, C. P. (2009). Protein and albimun-to-creatinine ratios in random urines accurately predict 24 h protein and albumin loss in patients with kidney disease. *Ann Clin Biochem*, *46*, 468-476. doi: 10.1258/acb.2009.009001

Hackam, D. G., Spence, J. D., Garg, A. X., & Textor, S. C. (2007). Role of renin-angiotensin system blockade in atherosclerotic renal artery stenosis and renovascular hypertension. *Hypertension*, *50*, 998-1003. doi: 10.1161/

Hirsch, S. (2008). An update on proteinuric chronic kidney disease: The dual-goal approach. *Cleveland Clinic Journal of Medicine, 75*, 705-713. doi: 10.3949/ccjm.75.10.705

Hunt, S. A., Abraham, W. T., Chin, M. H., Feldman, A. M., Francis, G. S., Ganiats, T. G., ...Yancy, C. W. (2009). Guidelines for the diagnosis and management of heart failure in adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, *119*, e404-e417.

Iqbal, R., & Shah, S. H. (2011). Diabetic nephropathy. *InnovAiT, 4*(12), 706-711. doi: 10.1093/innovait/inr081

Kakuta, H., Sudoh, K., Sasmata, M., & Yamagishi, S. (2005). Telmisartan has the strongest binding affinity to angiotensin II type I receptor: Comparison with other angiotensin II type I receptor blockers. *Int J Clin Pharmacol Res, 25*, 41–46.

Kloth, N., & Lane, A.S. (2011). ACE inhibitor-induced angioedema: A case report and review of current management. *Crit Care Resusc, 13(1)*, 33-7.

Krimholtz, M. J., Karalliedde, J., Thomas, S., Bilous, R., & Viberti, G. (2005). Targeting albumin excretion rate in the treatment of the hypertensive diabetic patient with renal disease. *JASN*, *16*(3), suppl 1 S42-S47.

Lizakowski, S., Rutkowski, P., Tylicki, L., Rutkowski, P., Renke, M., Sulikowska, B., ...Rutkowski, B. (2012). The effect of various types of the renin-angiotensin-aldosteron system blockade on proteinuria in chronic non-diabetic kidney disease: A double-blind cross-over randomised controlled trial. *Nephrol. Dial. Transplant, 27* (suppl 2), ii96-ii120. doi: 10.1093/ndt/gfs215

Loriga, G., Carru, C., Zinellu, A., Milia, A., & Satta, A. E.(2011). Renin angiotensin system inhibitors (rasi) and intima-media thickness (imt) in early-stage chronic kidney disease (CKD). *NDT Plus*, *4* (suppl 2), 4.s2.30. doi: 10.1093/ndtplus/4.s2.30.

Mancia, G., Schumacher, H., Redon, J., Verdecchia, P., Schmieder, R., Jennings, G., ...Yusuf, S. (2011). Blood pressure targets recommended by guidelines and incidence of cardiovascular and renal events in the ongoing telmisartan alone and in combination with ramipril global endpoint trial (ontarget). *Circulation, 124*, 1727-1736. doi: 10.1161/CIRCULATIONAHA.110.008870.

Mancia, G., & Corrao, G. (2009). Targeting blood pressure in the management of total cardiovascular risk. *European Heart Journal Supplements, 11*(Supplement F), F27-F32.

Masson, S., Latini, R., Milani, V., Moretti, L., Rossi, M. G., Carbonieri, E., ...GISSI-HF Investigators. (2010). Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: Data from the gissi-heartfailure trial. *Circ Heart Fail, 3*, 65-72. doi: 10.1161/CIRCHEARTFAILURE.109.881805

Muslih, A. I. (2012). Reduction of mean arterial pressure and proteinuria by the effect of aceis (lisinopril) in kurdish hypertensive patients in Hawler city. *Global Journal of Health Science*, 4(5), 1-2.

Ninomiya, T., Perkovic, V., de Galan, B. E., Zoungas, S., Pillai, A., Jardine, M., ...Chalmers, J. (2009). Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol, 20*,1813-1821.

Nordquist, L., Brown, R., Fasching, A., Persson, P., & Palm, F. (2009). Proinsulin C-peptide reduces diabetes-induced glomerular hyperfiltration via efferent arteriole dilation and inhibition of tubular sodium reabsorption. *Am J Physiol Renal Physiol, 297*, F1265-F1272. doi: 10.1152/ajprenal.00228.2009

O'Brien, E. (2008). Ambulatory blood pressure measurement: The case for implementation in primary care. *Hypertension, 51*, 1435-1441. doi: 10.1161/HYPERTENSIONAHA.107.100008

Özyilmaz, A., Bakker, S. J. L., de Zeeuw, D., de Jong, P. E., Gansevoort, R. T., & PREVEND Study Group. (2010). Selection on albuminuria enhances the efficacy of screening for cardiovascular risk factors. *Nephrol. Dial. Transplant, 25*, 3560-3568. doi: 10.1093/ndt/gfq478

Powers, B. J., Coeytaux, R. R., Dolor, R. J., Hasselblad, V., Patel, U. D., Yancy, Jr. W. S., ...Sanders, G. D. (2012). Updated report on comparative effectiveness of ace inhibitors, arbs, and direct renin inhibitors for patients with essential hypertension: much more data, little new information. *J Gen Intern Med, 27*(6), 716-729.

Rahmoni, K., Correia, M. L., Haynes, W. G., & Mark, A. L. (2005). Obesityassociated hypertension: New insights into mechanisms. *Hypertension, 45*, 9-14.

Rao, R. P., Jain, A. K., & Srinivasan, B. P. (2011). Dual therapy versus monotherapy of trandolapril and telmisartan on diabetic nephropathy in experimentally induced type 2 diabetes mellitus rats. *Journal of Renin-Angiotensin-Aldosterone System*, *12*, 169. doi: 10.1177/1470320310392097

Redding, K. M., Chen, B. L,, Singh, A., Re, R. N., Navar, L. G., Seth, D. M., ...Cook, J. L. (2010). Transgenic mice expressing an intracellular fluorescent fusion ofangiotensin II demonstrate renal thrombotic microangiopathy and elevated blood pressure. *Am J Physiol Heart Circ Physiol, 298*, 1807-1818. doi: 10.1152/ajpheart.00027.2010

Ruilope, L. M., & Bakris, G. L. (2011). Renal function and target organ damage in hypertension Eur. *Heart J*, *32*, 1599-1604. doi: 10.1093/eurheartj/ehr003

Russo, L. M., Osicka, T. M., Bonnet, F. Jerums, G., & Comper, W.D. (2002), Albuminuria in hypertension is linked to altered lysosomal activity and TGF-beta1 expression. *Hypertension*, *39*, 281-286.

Sarafidis, P., Tziolas, I., Zebekakis, P., Kanaki, A., itoglou-Makedou, A., Yovos, J., ...Lasaridis, A. (2007). Evaluation of the validity of albumin to creatinine ratio for the determination of low levels of urine albumin excretion in type 2 diabetic hypertensive subjects. *Nephrol. Dial. Transplant, 22*(suppl 6), 95-96.

Satchell, S.C., & Braet, F. (2009). Glomerular endothelial cell fenestrations: An integral component of the glomerular filtration barrier. *Am J Physiol Renal Physiol, 296*, 947-956. doi: 10.1152/ajprenal.90601.2008

Savelieva, I., Kakouros, N., Kourliouros, A., & Camm, A. J. (2011). Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. *Part I: primary prevention. Europace, 13*, 308-328. doi: 10.1093/europace/eur002

Sharpe, M., Jarvis, B., & Goa, K. L. (2001). Telmisartan: A Review of its Use in Hypertension. *Drugs, 61*(10), 1501-1529.

Shimizu, M., & Kario, K. (2008). Review: Role of the augmentation index in hypertension therapeutic advances in cardiovascular disease. *Ther Adv Cardiovasc Dis, 2,* 25-35. doi: 10.1177/1753944707086935

Song, J. C., & White, C. M. (2001). Olmisartan medoxomil (CS-866). An angiotensin II receptor blocker for treatment of hypertension. *Formulary, 36*, 485-500.

Tobe, S. W., Clase, C. M., Gao, P., McQueen, M., Grosshennig, A., Wang, X., ...Mann, J. F. E. (2011). Cardiovascular and renal outcomes with telmisartan, ramipril, or both in people at high renal risk: Results from the ontarget and transcend studies. *Circulation, 123*, 1098-1107. doi: 10.1161/CIRCULATIONAHA.110.964171

Tuncel, E., Erturk, E., Ersoy, C., Kıyıcı, S., Duran, C., Kuru, N., & Imamoglu, S. (2004). Physical activity alters urinary albumin/creatinine ratio in type 1 diabetic patient. *Journal of Sports Science and Medicine, 3*, 49-54

Verdecchia, P., Gentile, G., Angeli, F., & Reboldi, G. (2012). Beyond blood pressure: evidence for cardiovascular, cerebrovascular, and renal protective effects of renin–angiotensin system blockers. *Therapeutic Advances in Cardiovascular Disease, 6*, 81-91. doi: 10.1177/1753944712444866

White, W. B., Lacourciere, Y., Davidai, G. (2004). Effects of the angiotensin II receptor telmisartan versus valsartan on the circadian variation of blood pressure: Impact on the early morning period. *Am J Hypertens*, *17*, 347-353.

Yamagishi, S., Motsui, T., & Nakamura, K. (2008). Telmisartan inhibits advanced glycation end products (AGEs)-elicited endothelial cell injury by suppressing AGE receptor (RAGE) expression via peroxisome proliferator-activated receptor-γ activation. *Protein Pept Lett*, *15*, 850-853.

Yee, M. Mc., Jabbar, S. F., Osunkwo, I., Clement, L., Lane, P. A., Eckman, J. R., & Guasch, A. (2011). Chronic kidney disease and albuminuria in children with sickle cell disease. *Clin. J. Am. Soc. Nephrol, 6*, 2628-2633.

Zheng, Z., Lin, S., & Shi, H. (2010). A systematic review and meta-analysis of telmisartan vs valsartan in the management of essential hypertension. *The Journal Of Clinical Hypertension*, *12*(6)*,* 414-421. doi: 10.1111/j.1751-7176.2010.00287

