A Comparison of the Efficacy and Renal Side Effects of Antihypertensive Drugs "Angiotensin Receptor Blockers" (ARBs) in Rajavithi Hospital

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Background: *Hypertension is a major public health problem. As a result of the enforcement of measures announced by the National Drug Committee, the majority of original drugs is no longer prescribed and is replaced with drugs in the national list of essential medicines. Patients originally taking Angiotensin receptor blockers (ARBs) frequently have their prescription changed to generic losartan. Only a few studies have been conducted in Thailand to compare the efficacy and renal side effects of original and generic drugs.*

Objective: *To compare blood pressure (both systolic and diastolic) of patients who were changed to losartan from other ARBs.*

Material and Method: *A retrospective cross-sectional study was carried out, collecting data from medical records of patients with hypertension who were prescribed losartan instead of other ARBs in Rajavithi Hospital from 1 January 2009 to 31 December 2014. One hundred patients with hypertension during this period were enrolled, and the drugs' relative efficacies in controlling blood pressure were compared, together with their renal side effects.*

Results: *The study enrolled 100 patients, of which 35% were men, and the mean age was 66.88±10.93 years. The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) before and after changing from other ARBs to losartan showed a significant difference (134.16±12.89 vs. 140.92±11.76 mmHg, p-value <0.001) and (74.22±8.05 vs. 76.52±8.88 mmHg, p-value = 0.001, respectively). Other ARBs controlled hypertension significantly better than losartan (70.0% vs. 32.0%, p-value <0.001). Serum creatinine was significantly higher after changing the blood pressure lowering regimen (0.97±0.37 vs. 1.00±0.37 mg/dl, p-value = 0.047), but serum potassium levels did not change (4.27±0.40 vs. 4.27±0.32 mEq/L, p-value = 0.888).*

Conclusion: *Original ARBs controlled hypertension significantly better than losartan. Serum creatinine levels were lower when ARBs were prescribed rather than losartan; however, serum potassium levels were not affected.*

Keywords: *ARBs, Angiotensin receptor blockers, Hypertension, Renal function*

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Hypertension is a major public health problem worldwide and complications are higher in patients who do not achieve their target blood pressure. The eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood pressure (JNC 8)[1], which is the most recent guideline, recommends angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium-channel blockers (CCBs) and diuretics as the first line drugs in the treatment of hypertension.

The prevalence of hypertension increases from year to year, leading to rising costs in treating it. Currently, reimbursement is not permitted if a drug is not listed in the Thai National Drug Lists. The ARBs available in Thailand include candesartan, valsartan, irbesartan, olmesartan, telmisartan and losartan. Losartan is the only ARB included in the national list of essential drugs, and patients previously prescribed other ARBs are often switched to generic losartan. Many studies have shown that some patients have worse control of their blood pressure after changing ARBs, but a few studies[2] found no difference between other ARBs and losartan. Very little research has been conducted in Thailand to compare the efficacy and

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renal side effects of losartan and other ARBs.

Material and Method

A retrospective review was performed using ICD-10 code I10 of outpatients' medical records to identify patients diagnosed with hypertension who received original ARB drugs before being switched to losartan. Blood pressure levels, serum creatinine and serum potassium were measured before and after the change of drugs. The protocol of this research was reviewed and approved by the ethics committee of Rajavithi Hospital (No. 27/2558).

Study populations

The present study reviewed the outpatient medical records of patients diagnosed with hypertension between January 2009 and December 2014. Hypertensive patients of either sex were eligible for inclusion in the present study if they were at least 18 years of age. The patients included had received other ARBs for at least 8 weeks before the change to losartan, had had no other changes in medication, and had made at least four regular outpatient visits before and after the drug switch. Patients were excluded if there was irregular follow-up or if they had had any change in other medication.

Study protocol

Baseline characteristics such as age, sex, co-morbid diseases and prescribed drugs were collected. Blood pressure, and serum creatinine and potassium levels were recorded both before and after the change from other ARBs to losartan.

Blood pressure levels were measured with automated sphygmomanometers, and medical outpatient records were used in the analysis. Average systolic blood pressure (SBP), average diastolic blood pressure (DBP), and serum creatinine and potassium levels were recorded.

Controlled hypertension was defined as both SBP <140 mmHg and DBP <90 mmHg at each of the last 3 visits before and after changing antihypertensive medicine. Acute kidney injury was defined as an increase in serum creatinine of $\geq$0.3 mg/dl from the baseline. Hyperkalemia was defined as serum potassium of $\geq$5.0 mEq/L.

Outcomes

The primary endpoint was to determine whether there was a difference in the average SBP and DBP before and after losartan was prescribed. The secondary endpoint was to determine whether there was a difference in well controlled hypertension, serum creatinine and serum potassium levels before and after losartan was prescribed.

Statistical analysis

The estimated sample size was based on previous studies[3]. Using a 2-sided type I error of 5%, 90% power and corrected with patients numbers in hospital, a sample size of 95 patients was required.

Baseline characteristics were described as number (percentage), mean$\pm$SD. Chi-square test/ Fisher's exact test were employed to test the difference in qualitative variables, whereas 2-sample t-test was used for quantitative variables and Mann Whitney U test was used for non-normal distribution with a *p*-value <0.050 using the SPSS for Windows program, version 17.

Results

From January 1, 2009 to December 31, 2014 100 patients with hypertension who received other ARBs and were switched to losartan were enrolled in the present study.

The baseline characteristics, (Table 1), show that the majority of participants were female and the mean age was 66.88$\pm$10.93 years. Co-morbidities were mainly diabetes mellitus and dyslipidemia, and a few patients had chronic kidney disease and coronary artery disease. The most commonly used ARBs before the switch to losartan were candesartan, irbesartan and valsartan.

The SBP and DBP from four visits before and after losartan was prescribed are shown in Table 2. The average SBP and DBP while taking other ARBs were significantly lower than after the switch to losartan (134.16$\pm$12.89 mmHg vs. 140.92$\pm$11.76 mmHg, *p*-value <0.001, and 74.22$\pm$8.05 mmHg vs. 76.52$\pm$8.88 mmHg, *p*-value = 0.001, respectively).

When determining the adequacy of blood pressure control, 70% of the patients on other ARBs had controlled hypertension, while after switching the medication to losartan, the proportion of patients with controlled hypertension decreased to 32.0% (*p*-value <0.001) as shown in Table 3. With regard to patients with previously uncontrolled hypertension, most of them remained uncontrolled after changing to losartan, and only 13.33% of patients had controlled blood pressure (odds ratio for other ARBs/losartan to controlled hypertension was 4.96 (95% CI 2.72-9.03).

Of the 100 patients, only 81 had records of

serum creatinine both before and after the change in medication. After the change, 19 patients showed a decrease in serum creatinine, 30 patients were unchanged, and 32 patients showed an increase. Only four patients had acute kidney injury, and two patients in this group had known chronic kidney disease. Average creatinine in patients with other ARBs was 0.97±136 mg/dl, and after switching to losartan it was 1.00±0.37 mg/dl (*p*-value = 0.047).

Table 1. Baseline characteristics and ARBs drug received

Characteristics	n = 100
Female, n (%)	65 (65.0)
Age (years), mean ± SD	66.88±10.93
Comorbid disease	
Diabetes mellitus, n (%)	43 (43.0)
Dyslipidemia, n (%)	68 (68.0)
Chronic kidney disease, n (%)	9 (9.0)
Congestive heart failure, n (%)	1 (1.0)
Coronary heart disease, n (%)	9 (9.0)
Drug	
Candesartan 16 mg, n (%)	32 (32.0)
Irbesartan 300 mg, n (%)	20 (20.0)
Telmisartan 80 mg, n (%)	14 (14.0)
Valsartan 160 mg, n (%)	13 (13.0)
Valsartan/HCTZ 160/25 mg, n (%)	12 (12.0)
Olmesartan 40 mg, n (%)	7 (7.0)
Candesartan/HCTZ 8/12.5 mg, n (%)	1 (1.0)
Losartan/HCTZ 100/25 mg, n (%)	1 (1.0)

HCTZ = Hydrochlorothiazide

Serum potassium levels in 76 patients were measured and the average did not differ significantly before and after changing medication (4.27±0.40 vs. 4.27±0.32 mEq/L, respectively, *p*-value = 0.888). Only four patients had mild hyperkalemia with other ARBs, and all of these had chronic kidney disease. After changing to losartan, four patients had hyperkalemia: three of these had it before the change, while one developed it and another returned to normal serum potassium levels after the switch to losartan.

Discussion

In most previous studies, blood pressure control was compared between patients prescribed losartan and those who took other ARB drugs such as candesartan[2-9], valsartan[10,11], irbesartan[10,12,13], olmesartan[10] and telmisartan[14,15]. The results showed that other ARB drugs achieved better results than losartan in controlling blood pressure levels both at daytime and at nighttime[16]. The patients in studies who received crossover of medicine[14] also showed that other ARBs were more effective than losartan in controlling hypertension. A few previous studies showed no difference in blood pressure control between patients taking candesartan[9] or valsartan[11] versus losartan, but patients who received candesartan showed better clinical outcomes than those who used losartan. One real-world primary care practice study[17] showed that patients who switched medication from losartan to candesartan had significantly lower blood pressure 2 years after the switch. This study

Table 2. Comparison of blood pressure levels between patients receiving other ARBs and those prescribed losartan

Blood pressure level	Before (other ARBs) Mean ± SD	After (losartan) Mean ± SD	*p*-value
Systolic blood pressure			
Visit 1 (mmHg)	132.19±16.76	143.68±16.75	<0.001*
Visit 2 (mmHg)	135.01±16.64	139.40±14.42	0.042*
Visit 3 (mmHg)	136.16±15.43	141.64±16.88	0.008*
Visit 4 (mmHg)	133.28±15.00	138.97±17.47	0.005*
Average (mmHg)	134.16±12.89	140.92±11.76	<0.001*
Diastolic blood pressure			
Visit 1 (mmHg)	73.50±10.62	78.29±13.14	<0.001*
Visit 2 (mmHg)	74.93±12.98	75.47±11.43	0.713
Visit 3 (mmHg)	74.78±10.33	77.44±12.54	0.053
Visit 4 (mmHg)	73.65±10.32	74.88±11.62	0.314
Average (mmHg)	74.22±8.05	76.52±8.88	0.001*

ARBs = Angiotensin receptor blockers
* = Significant at $p<0.050$

demonstrated that patients taking other ARBs had lower blood pressure levels and more controlled hypertension than patients taking losartan did, and this is similar to the findings of many previous studies. More controlled hypertension may result in lower major adverse cardiovascular events. Previous research[18] has shown the cost effectiveness of other ARBs, which lower diastolic blood pressure more effectively than losartan, and other ARBs may actually be more cost effective than losartan in cardiovascular prevention. In this present study, ARBs other than losartan attained better control of blood pressure, and this may reduce the number of adverse cardiovascular events. However, this study did not have a long-term follow-up to show any benefits in terms of cardiovascular outcome.

As to renal side effects, there were some differences in impact on serum creatinine levels, but serum potassium levels were largely unchanged. The present study showed that patients taking other ARBs had significantly lower serum creatinine than those taking losartan. Previous research has shown contrasting results: some studies showed that patients taking other ARBs had more elevation of serum creatinine than those prescribed losartan[19] while others found no difference[20]. In the present study, patients taking other ARBs had significantly lower serum creatinine levels than those taking losartan. However, the rise in the level of serum creatinine in the two groups from 0.97 mg/dl to 1.00 mg/dl may be co-incidental due to the small sample size or missing data and this requires further investigation. The occurrence of acute kidney injury was did not differ in the two groups.

Serum potassium levels were unchanged after switching medication to losartan, similar to the findings of previous studies[20]. In the present study, four patients had hyperkalemia and all of these had known chronic kidney disease; this finding was unchanged after switching medication. Doctors should be reminded of the need to check serum potassium levels after prescribing ARBs, especially in patients with known chronic kidney disease.

Table 3. Comparison of number of patients with controlled hypertension between other ARBs and losartan

	Controlled hypertension		*p*-value
	Yes	No	
Before (other ARBs)	70 (70.0)	30 (30.0)	<0.001*
After (losartan)	32 (32.0)	68 (68.0)	

ARBs = Angiotensin receptor blockers
* = Significant at $p<0.050$

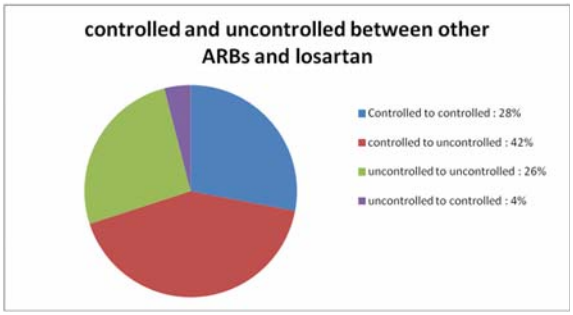

Fig. 1 Controlled and uncontrolled hypertension between patients taking other ARBs and those prescribed losartan.

Limitations

The present research was a retrospective study reviewing medical records, some of which had incomplete data about serum creatinine and potassium. Patients without regular follow-up were excluded from this study, and this may have caused selection bias; in addition, other factors that may have affected blood pressure and renal side effects were not measured. The present study measured only surrogate endpoints and the sample size was too small to show an effect on major adverse cardiovascular outcome. Further investigation with a larger sample size and long-term follow-up is needed to determine effects on clinical endpoints.

Conclusion

The other original ARBs group lowered both systolic and diastolic blood pressure more effectively than losartan, and more patients taking other ARBs had controlled hypertension. Serum creatinine levels were lower in patients taking other ARBs than in those prescribed with losartan; however, the incidences of acute kidney injury and serum potassium levels were not significantly different.

What is already known on this topic ?

Hypertension was the major public health care and angiotensin receptor blockers were the choice of blood pressure control.

Controversy in efficacy between original other ARBs and losartan, some studies showed different in blood pressure control but other studies did not different.

Most recent studies were case-control compared efficacy between other ARBs and losartan. Few studies, to assess efficacy in patients who switch medication from other ARBs to losartan including Thailand.

Clinicians were hesitated about efficacy to adjusted other ARBs to losartan from announcement of the National drug committee.

What does this study adds ?

The other original ARBs group can lower both systolic and diastolic blood pressure greater than losartan and more patients had controlled hypertension.

Serum creatinine level was lower in other ARBs than in losartan but the incidence of acute kidney injury and serum potassium level were not different.

Few patients who know chronic kidney disease had hyperkalemia; the patients who have chronic kidney disease should check serum potassium before and after receiving ARBs drug.

Potential conflicts of interest

None.

References

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014; 311: 507-20.
2. Manolis AJ, Grossman E, Jelakovic B, Jacovides A, Bernhardi DC, Cabrera WJ, et al. Effects of losartan and candesartan monotherapy and losartan/hydrochlorothiazide combination therapy in patients with mild to moderate hypertension. Losartan Trial Investigators. Clin Ther 2000; 22: 1186-203.
3. Gradman AH, Lewin A, Bowling BT, Tonkon M, Deedwania PC, Kezer AE, et al. Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. Candesartan Versus Losartan Efficacy Comparison (CANDLE) Study Group. Heart Dis 1999; 1: 52-7.
4. Lacourciere Y, Asmar R. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: a placebo-controlled, forced titration study. Candesartan/Losartan study investigators. Am J Hypertens 1999; 12: 1181-7.
5. Bakris G, Gradman A, Reif M, Wofford M, Munger M, Harris S, et al. Antihypertensive efficacy of candesartan in comparison to losartan: the CLAIM study. J Clin Hypertens (Greenwich) 2001; 3: 16-21.
6. Vidt DG, White WB, Ridley E, Rahman M, Harris S, Vendetti J, et al. A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II. J Hum Hypertens 2001; 15: 475-80.
7. Baguet JP, Nisse-Durgeat S, Mouret S, Asmar R, Mallion JM. A placebo-controlled comparison of the efficacy and tolerability of candesartan cilexetil, 8 mg, and losartan, 50 mg, as monotherapy in patients with essential hypertension, using 36-h ambulatory blood pressure monitoring. Int J Clin Pract 2006; 60: 391-8.
8. Meredith PA, Murray LS, McInnes GT. Comparison of the efficacy of candesartan and losartan: a meta-analysis of trials in the treatment of hypertension. J Hum Hypertens 2010; 24: 525-31.
9. Kjeldsen SE, Stalhammar J, Hasvold P, Bodegard J, Olsson U, Russell D. Effects of losartan vs candesartan in reducing cardiovascular events in the primary treatment of hypertension. J Hum Hypertens 2010; 24: 263-73.
10. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. J Clin Hypertens (Greenwich) 2001; 3: 283-91, 318.
11. Elliott WJ, Calhoun DA, DeLucca PT, Gazdick LP, Kerns DE, Zeldin RK. Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial. Clin Ther 2001; 23: 1166-79.
12. Dang A, Zhang Y, Liu G, Chen G, Song W, Wang B. Effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia in Chinese population. J Hum Hypertens 2006; 20: 45-50.
13. Kassler-Taub K, Littlejohn T, Elliott W, Ruddy T, Adler E. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan in mild-to-moderate hypertension. Irbesartan/Losartan Study Investigators. Am J Hypertens 1998; 11: 445-53.
14. Fogari R, Mugellini A, Zoppi A, Derosa G, Rinaldi A, Fogari E, et al. Efficacy of losartan, valsartan,

and telmisartan in patients with mild to moderate hypertension: a double-blind, placebo-controlled, crossover study using ambulatory blood pressure monitoring. Curr Ther Res 2002; 63: 1-14.
15. Smith DH, Cramer MJ, Neutel JM, Hettiarachchi R, Koval S. Comparison of telmisartan versus losartan: meta-analysis of titration-to-response studies. Blood Press Monit 2003; 8: 111-7.
16. Barreras A, Gurk-Turner C. Angiotensin II receptor blockers. Proc (Bayl Univ Med Cent) 2003; 16: 123-6.
17. Usher-Smith J, Ramsbottom T, Pearmain H, Kirby M. Evaluation of the clinical outcomes of switching patients from atorvastatin to simvastatin and losartan to candesartan in a primary care setting: 2 years on. Int J Clin Pract 2008; 62: 480-4.
18. Simons WR. Comparative cost effectiveness of angiotensin II receptor blockers in a US managed care setting: olmesartan medoxomil compared with losartan, valsartan, and irbesartan. Pharmacoeconomics 2003; 21: 61-74.
19. Rayner BL, Trinder YA, Baines D, Isaacs S, Opie LH. Effect of losartan versus candesartan on uric acid, renal function, and fibrinogen in patients with hypertension and hyperuricemia associated with diuretics. Am J Hypertens 2006; 19: 208-13.
20. Williams M, Sease J. Equivalent dosing of irbesartan, valsartan, and losartan identified through formulary switch at a Veterans Affairs Medical Center. Formulary 2008; 43: 14-20.

การเปรียบเทียบประสิทธิภาพและผลข้างเคียงต่อไตของยาลดความดันโลหิตสูงกลุ่ม angiotensin receptor blockers (ARBs) ในผู้ป่วยโรงพยาบาลราชวิถี

สุรพันธ์ พงศ์สุธนะ, กิตติวัฒน์ ฉัตรพงศ์ธาดา

ภูมิหลัง: โรคความดันโลหิตสูงเป็นปัญหาสุขภาพที่สำคัญ และเนื่องจากมีการประกาศนโยบายการใช้ยา โดยแนะนำให้ใช้ยาในบัญชียาหลักแห่งชาติก่อนเป็นอันดับแรก จึงมีการเปลี่ยนยาจากยา ARBs ชนิดอื่นมาเป็น losartan ซึ่งในประเทศไทยยังมีการศึกษาไม่มากนัก ดังนั้นผู้นิพนธ์จึงเลือกศึกษาถึงประสิทธิภาพและผลข้างเคียงของไตระหว่างยา ARBs ชนิดอื่นๆ กับ losartan

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิภาพในการควบคุมความดันโลหิต (ทั้งความดันซิสโตลิกและความดันไดแอสโตลิก) ก่อนและหลังเปลี่ยนจากยา ARBs ชนิดอื่นๆ เป็น losartan

วัสดุและวิธีการ: เป็น retrospective cross-sectional study โดยเก็บข้อมูลจากเวชระเบียนผู้ป่วยที่ได้รับวินิจฉัยโรคว่าเป็นความดันโลหิตสูง และมีการเปลี่ยนแปลงการได้รับยาลดความดันโลหิตจาก ARBs ชนิดอื่นๆ มาเป็น losartan ที่รักษาในโรงพยาบาลราชวิถี ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2553 ถึง 31 ธันวาคม พ.ศ. 2557 จำนวนทั้งหมด 100 คน โดยศึกษาเปรียบเทียบประสิทธิภาพการลดความดันโลหิตและผลข้างเคียงทางไต ก่อนและหลังการเปลี่ยนยา ARBs

ผลการศึกษา: มีผู้ป่วยเข้าร่วมการศึกษาจำนวน 100 คน เป็นเพศชายร้อยละ 35 อายุเฉลี่ย 66.88±10.93 ปี มีความดันโลหิตซิสโตลิกเฉลี่ยก่อนและหลังเปลี่ยนยาเป็น losartan แตกต่างกันอย่างมีนัยสำคัญ (134.16±12.89 เทียบกับ 140.92±11.76 มม.ปรอท ตามลำดับ, p-value <0.001) และความดันโลหิตไดแอสโตลิกเฉลี่ยแตกต่างกัน (74.22±8.05 เทียบกับ 76.52±8.88 มม.ปรอท ตามลำดับ, p-value = 0.001) เมื่อดูเรื่องการควบคุมความดันโลหิตได้ตามเกณฑ์พบว่าในกลุ่มที่ใช้ยา ARBs ชนิดอื่นสามารถควบคุมได้ดีกว่า losartan อย่างมีนัยสำคัญ (ร้อยละ 70.0 เทียบกับร้อยละ 32.0 ตามลำดับ, p-value <0.001) มีระดับครีตินีนในเลือดแตกต่างกันระหว่างก่อนและหลังเปลี่ยนยาเป็น losartan อย่างมีนัยสำคัญ (0.97±0.37 เทียบกับ 1.00±0.37 มก./ดล. ตามลำดับ, p-value = 0.047) แต่ไม่มีความแตกต่างกันในเรื่องระดับโพแตสเซียม (4.27±0.40 เทียบกับ 4.27±0.32 mEq/L ตามลำดับ, p-value = 0.888)

สรุป: ยาในกลุ่ม ARBs ชนิดอื่นสามารถที่จะควบคุมระดับความดันโลหิตได้ดีกว่าและมีระดับของครีตินีนในเลือดต่ำกว่าการใช้ยา losartan อย่างมีนัยสำคัญทางสถิติแต่ไม่แตกต่างกันในเรื่องระดับโพแตสเซียมในเลือด