Japan-Indonesia Collaborative Study of Imidapril on Antiproteinuric Effect in Hypertensive Patients with Chronic Kidney Disease (CKD)

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Background : Chronic kidney disease (CKD) is a comprehensive disease concept that includes chronic glomerulonephritis such as IgA nephropathy or lupus nephritis, diabetic nephropathy and hypertensive nephrosclerosis. CKD is a risk factor for end stage kidney disease (ESKD) and cardiovascular diseases (CVD). It is considered that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) induce a marked renoprotective effect in patients with CKD. The purpose of the present Japan-Indonesia collaborative study was to evaluate the antiproteinuric effect of imidapril, one of the ACEIs, in hypertensive patients with CKD.

Methods : Twenty three hypertensive CKD patients were treated with imidapril and a calcium channel blocker (CCB). Imidapril was added for patients who had been treated with a CCB such as diltiazem at the start of this study. When blood pressure (BP) did not reach the target level ($<130/85$ mmHg), imidapril dosage was increased to 10 mg/day and administered for 12 months. Alternatively, patients were treated with 5-10 mg/day of imidapril.

Results : In the imidapril + CCB combination therapy, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly reduced, both at 6 months and at the end of the clinical study. Only DBP reached values below the target level. Urinary albumin excretion (UAE) levels were markedly decreased at 6 and 12 months when compared with the baseline values (0.45 ± 0.54 g/g·Cr indicating typical overt proteinuria) and these decreases at both time points were significant. The UAE levels at both 6 and 12 months complied with the diagnostic criteria for microalbuminuria (< 0.299 g/g·Cr).

Conclusion : In this collaborative study, a combination of imidapril and a CCB, such as diltiazem, significantly reduced BP, and reduced UAE, suggesting strict BP control may induce an efficient decrease in UAE. It appears that imidapril-based therapy has renoprotective effects in hypertensive patients with CKD.

Key words : proteinuria, blood pressure, imidapril (ACE inhibitor), CKD, Japan-Indonesia

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Introduction

Chronic Kidney Disease (CKD) is a comprehensive disease concept that includes chronic glomerulonephritis such as IgA nephropathy or lupus nephritis, diabetic nephropathy and hypertensive nephrosclerosis, as well as a variety of renal diseases including but not limited to dialysis and kidney transplantation¹⁾. The concept of CKD has recently been proposed and is steadily spreading as a new condition jeopardizing the human health²⁾. In Japan, comprehensive CKD measures have been inclusively taken on Japanese Society of Nephrology, and also, Asian countries have been taken steps to against CKD. However, the research works is not enough in Asian countries, especially Southeast Asian countries. The purpose of the present study is to activate the CKD clinical research in Indonesia through this collaborative study.

As it progresses, CKD induces histological renal changes that are usually irreversible and cause glomerulosclerosis and tubular interstitial fibrosis, leading to end stage kidney disease (ESKD). High risk groups for CKD requiring particular attention include those with diabetes mellitus, hypertension, metabolic syndrome, obesity, cigarette smoking, family history of CKD and dyslipidemia³⁾. In CKD patients, hypertension occurs with high frequency as a complication, and hypertension itself, as in the case of proteinuria or decreased GFR, is a strong risk factor for progression of renal function impairment^{4) 5)}. On the other hand, hypertension is also a strong risk factor for development and progression of cardiovascular diseases (CVD)⁶⁾. To break this vicious spiral, it is necessary to start proactive control of blood pressure (BP) early in the management of CKD.

Clinical practice guidelines for management of hypertension in Japan (JSH 2004)⁷⁾, Europe (ESH/ESC 2007)⁸⁾, and the USA (JNC7)⁹⁾ recommend ACE inhibitors or ARBs as first-line therapy on the basis of results of large-scale clinical studies such as AASK¹⁰⁾ and RENAAL¹¹⁾. Imidapril hydrochloride is a long-acting ACE inhibitor with no sulfhydryl group, for which renoprotective effects, including reduction of proteinuria, have been dem-

onstrated in Dahl rats¹²⁾ and in rats given NOS inhibitors¹³⁾. Furthermore, in clinical trials conducted in Japan, imidapril has been shown to prevent the increase of UAE in micro- and macroalbuminuric patients with type 1 diabetes mellitus with the target BP set at less than 130/80 mmHg¹⁴⁾. With this background, we evaluated renoprotective effects of imidapril in CKD patients by investigating systolic and diastolic blood pressure (SBP/DBP), UAE and serum creatinine (sCr) in a Japan- Indonesia Collaborative Study. Since hypertension that occurs as a complication of CKD is known to be serious and refractory, monotherapy frequently fails to reduce BP to the target levels. Given this concern, and in expectation of effects beyond BP lowering, imidapril was administered in combination with a CCB.

Patients and Method

Patients

This study was conducted in Japan and Indonesia in accordance with the principles of the Declaration of Helsinki. All CKD (stage 1-3)³⁾ patients provided informed consent after receiving a detailed explanation of the study. Twenty three patients (male 10 patients, female 10 patients and unknown 3 patients) with a mean age of 60.5 y. o were enrolled. Among them, 16 patients were non-diabetes and 7 patients were diabetes mellitus. Further, 7 patients were at Juntendo University, 6 patients at Indonesia University, and 10 patients at Ailangga University. The course of study parameters at baseline and after completion of treatment (from 6 months to 12 months) is shown in Table-1.

Study subject selection was conducted based on screening of laboratory data, medical histories and current medical status. These patients who met the following inclusion criteria but none of the exclusion criteria were ultimately enrolled : a history of hypertension ($130 \leq \text{sitting SBP} < 180 \text{ mmHg}$, $85 \leq \text{sitting DBP} < 110 \text{ mmHg}$) ; serum creatinine (sCr) $< 2.0 \text{ mg/dL}$; and urinary albumin excretion (UAE) $< 1 \text{ g/24 hrs}$. The exclusion criteria included patients with contraindications such as pregnancy, renovascular hypertension, or angioma ; need for careful administration of ACE inhibitors or ARBs such as patients with severe hyperten-

Table-1 Characteristics of 23 chronic kidney disease patients who received imidapril with CCB

	(Mean $\pm$ SD)
Age(yrs)	60.5 $\pm$ 10.5
Blood pressure(mmHg)	
SBP	147 $\pm$ 14
DBP	87 $\pm$ 10
Urinary albumin excretion(g/g·Cr)	0.45 $\pm$ 0.54
Serum creatinine(mg/dL)	1.01 $\pm$ 0.36

CCB: calcium channel blocker

Table-2 Effects of imidapril + CCB therapy on blood pressure (BP) and renal function in 21 chronic kidney disease patients

	SBP (mmHg)	DBP (mmHg)	UAE (g/g·Cr)	sCr (mg/dL)
Baseline	147 $\pm$ 14	87 $\pm$ 10	0.45 $\pm$ 0.54	1.01 $\pm$ 0.36
6month	135 $\pm$ 14*	80 $\pm$ 8*	0.20 $\pm$ 0.30*	1.03 $\pm$ 0.34
12month	133 $\pm$ 16*	80 $\pm$ 8*	0.15 $\pm$ 0.26*	1.07 $\pm$ 0.35

CCB:calcium channel blocker

SBP:systolic blood pressure

DBP:diastolic blood pressure

UAE:Urinary Albumin Excretion

sCr:Serum Creatinine

sion ; patients who undergo hemodialysis ; patients on diuretic therapy (especially those in whom diuretic therapy has been recently initiated) ; patients on strict dietary salt restriction ; diabetic patients with obviously poor glucose control ($\text{HbA1c} \geq 10\%$) and patients judged by the attending physician to be inappropriate, i. e. patients with kidney transplantation or proteinuria >1.0 g/24 hrs.

Treatment protocol

Twenty three patients were treated with imidapril and CCB. Imidapril was added for patients who had been treated with a CCB such as diltiazem at the start of this study. When BP did not reach the target level ($<130/85$ mmHg), imidapril dosage was increased to 10 mg/day and administered for 12 months. Alternatively, patients were first treated with 5–10 mg/day of imidapril. In principle, antihypertensive drugs such as diuretics, which had been prescribed before this study, were not changed during the study. All patients in this study underwent bi-monthly laboratory check-ups throughout the 12-month study period.

Figure-1 UAE levels were markedly decreased at 6 and 12 months when compared with the baseline values ($p < 0.05$).

Evaluation and Measurement

At 2 weeks before initiation of the study (baseline) and at the beginning of every 2-month period, SBP/DBP, sCr and UAE were measured in each patient. BP was measured using a mercury sphygmomanometer with the patient in the sitting position.

Statistical analysis

Results are expressed as means $\pm$ SD. Paired t-test and two-way ANOVA were used to evaluate changes from baseline of sCr, UAE, and SBP/DBP. P values < 0.05 were considered significant.

Results

In the imidapril + CCB combination therapy, the average SBP and DBP at baseline were 147 ± 14 mmHg and 87 ± 10 mmHg, respectively. SBP and DBP were significantly reduced, both at 6 months and at the end of the clinical study at 12 months. Only DBP reached values below the target level (Table-2).

In the imidapril + CCB combination therapy, UAE levels were markedly decreased at 6 and 12 months when compared with the baseline values (0.45 ± 0.54 g/g·Cr indicating typical overt proteinuria) and these decreases at both time points were significant. The UAE levels at both 6 and 12 months complied with the diagnostic criterion for microalbuminuria (<0.299 g/g·Cr) based on quantitative evaluation of spot urine samples as proposed

by the Japanese CKD guidelines¹⁵⁾. sCr showed no significant changes (Fig-1)

Discussion

In Japan, definitions of CKD were published in the Clinical Practice Guidelines for Diagnosis and Treatment of CKD (2007) and the Clinical Practice Guidelines for Diagnosis and Treatment of CKD – With Special Reference to Hypertension (2008). The first objective of the present Japan-Indonesia Collaborative Study was used to follow the progression of renal function impairment. The following measures have been proposed to prevent CKD from progressing to end stage kidney disease (ESKD) : 1) lifestyle modification (improvements in obesity, dyslipidemia and hyperglycemia), 2) diet therapy, 3) control of hypertension, 4) suppression of the renin-angiotensin system (RAS), 5) improvement of anemia, and 6) elimination of uremic toxins³⁾. Among these measures, the RAS plays an important role in regulating BP. Blockade of the RAS with ACE inhibitors or ARBs has been shown to be effective treatment for hypertension^{16) 17)}.

Independent of their ability to lower BP, these agents have also been reported to be associated with the progression of nephropathy in patients with diabetes mellitus and chronic renal failure^{18)~21)}.

Although the guidelines for the management of hypertension^{7)~9)} recommend that BP should be strictly controlled in hypertensive patients with renal diseases, adequate BP levels are not often achieved with RAS inhibitor monotherapy. A combination of two to three antihypertensive agents is required to decrease BP to target levels, especially in patients with renal diseases²²⁾. The main candidates for combination with a RAS inhibitor include CCBs, since they reduce BP even in patients who are considered resistant to other antihypertensive agents²³⁾. In addition, it is known that non-dihydropyridine (DHP) CCBs such as diltiazem show BP independent renoprotective effects²⁴⁾. Especially in patients with diabetes, nifedipine significantly increased proteinuria and significantly decreased creatinine clearance (CCr) when compared with diltiazem²⁵⁾. In another study, diltiazem decreased proteinuria in patients with diabetes and its effect was similar to that of lisinopril²⁶⁾. Therefore, a

more potent renoprotective effect may be achieved with imidapril with diltiazem. Imidapril is a versatile ACE inhibitor that has been used clinically in the treatment of hypertension, chronic congestive heart failure and acute myocardial infarction²⁷⁾. In addition, imidapril, like other ACE inhibitors, alleviates renal injuries in rat models of various types of nephropathy^{12) 28)}, and has been shown to inhibit renal ACE activity more potently than captopril or enalapril^{29)~31)}. Therefore, imidapril may have advantages over other antihypertensive agents in protecting against renal damage. The Guidelines for Management of Hypertension 2009 (JSH 2009)³²⁾ recommend that even in patients with high-normal BP of 130-139/85-89 mmHg, the presence of CKD and diabetes mellitus requires application any effective antihypertensive therapy to maintain BP at normal levels. According to the Clinical Practice Guidelines for Diagnosis and Treatment of CKD, with Special Reference to Hypertension (2008)¹⁵⁾, the target BP for antihypertensive treatment in CKD patients with hypertension as a complication is <130/80 mmHg, and is even lower (<125/75mmHg) if proteinuria is ≥ 1 g/day.

We evaluated the results of this collaborative study based on disease conditions to be treated and target BP for antihypertensive treatment recommended by both of the above-mentioned guidelines, i. e. JSH 2009 Guidelines and Clinical Practice Guidelines for CKD. In the imidapril + CCB combination therapy, the baseline SBP/DBP of the combination therapy group on the whole was $147 \pm 14 / 87 \pm 10$ mmHg, which satisfied the conditions requiring treatment proposed by the two guidelines, and met the inclusion criteria of the collaborative study. The baseline UAE level was 0.45 ± 0.54 g/g·Cr, which clearly indicated overt proteinuria. The average SBP/DBP values at 6 and 12 months after the start of combination therapy were $135 \pm 14 / 80 \pm 8$ and $133 \pm 16 / 80 \pm 8$ mmHg, respectively. Both SBP and DBP were significantly reduced, although only DBP reached the target BP level for CKD (<130/80mmHg) at both 6 and 12 months. The significant reduction in DBP at both 6 and 12 months after the start of combination therapy was reflected in UAE, which was significantly decreased to 0.20 ± 0.30 and 0.15 ± 0.26 g/g·Cr, respectively. Thus, improvement from overt protei-

nuria to microalbuminuria was clearly noted. Shigihara *et al.*³³⁾ demonstrated that in hypertensive microalbuminuric type 2 diabetic patients, the combination of an ACE inhibitor (including imidapril) and a CCB (amlodipine) resulted in marked reduction in BP (DBP<80mmHg) and greater decrease in UAE than use of an ACE inhibitor alone. Our results were consistent with this finding and in the Collaborative Study imidapril with CCB combination therapy exerted a greater antiproteinuric effect than imidapril alone in the CKD subgroup in which DBP fell below the target level (data not shown). Recently, much attention has been paid to the strategy for prevention of the progression of CKD. By accumulating data from a large number of clinical mega-trials, we have witnessed the beneficial action of ACE inhibitors^{20) 34) 35)}. On the basis of previously reported findings on efficacy of an ACE inhibitor and CCB combination strategy for the management of CKD^{33) 36) 37)}, together with the results of this collaborative study, a CCB may be the best candidate for combination with an ACE inhibitor for the treatment of CKD.

In this collaborative study, combination treatment with imidapril and a CCB, such as diltiazem, significantly reduced BP, and reduced UAE, suggesting that strict BP control may induce an efficient decrease in UAE. In addition, the level of serum creatinine (sCr) did not increase during this study. It appears that imidapril-based therapy has renal protective effects in patients with various chronic kidney diseases. Further study which is controlled, double-blinded and randomized with larger number of patients is necessary to investigate ACE-I + CCB combination for treatment of CKD.

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Conflict of interest statement : None declared.

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Review

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Effect in Hypertensive Patients with Chronic Kidney Disease (CKD)

CKD患者におけるイミダプリルの尿蛋白減少効果

(日本—インドネシア共同研究)

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抄 録

背景：慢性腎臓病（CKD）は、IgA腎症やループス腎炎などの慢性糸球体腎炎、糖尿病腎症や腎硬化症など、全ての慢性腎臓病を含んだ疾患概念である。CKDは末期腎不全（ESKD）の準備状態であると同時に、心血管疾患（CVD）の重大なリスク因子であることが明らかとなっている。アンジオテンシン変換酵素（ACE）阻害薬やアンジオテンシンⅡ受容体拮抗薬（ARB）は、降圧薬として広く用いられているが、両薬剤の腎保護効果にも注目が集まっている。今回、順天堂大学とインドネシア大学、アイルランガ大学は、高血圧を伴うCKD患者におけるACE阻害薬イミダプリルの尿蛋白減少効果を検討する共同研究を行った。

方法：23名の高血圧を伴うCKD患者にカルシウム拮抗薬（CCB）とイミダプリルを投与し、腎機能と尿蛋白量の変化を治療前後で比較した。CCBを投与している患者にイミダプリルを追加投与（5mg/日）し、血圧が目標値（130/85mmHg未満）に達しなかった場合には、さらにイミダプリルを10mg/日まで増量し、投与後12ヵ月で評価した。

結果：CCBにイミダプリルを加えることによって、6ヵ月後・12ヵ月後の収縮期血圧および拡張期血圧は有意に低下した。尿中アルブミン排泄量は、投与開始時には顕性蛋白尿レベル（0.3g/g・Cr以上）であったが、6ヵ月後・12ヵ月後は共に微量アルブミン尿レベル（0.299g/g・Cr以下）にまで有意に減少した。

結語：イミダプリルとCCBの併用によるCKD患者の腎保護効果を、順天堂大学とインドネシア大学、アイルランガ大学の共同研究により検討した。イミダプリルを軸とした治療により、CKD患者の血圧は有意に低下し、尿中アルブミン排泄量は有意に減少した。以上より、イミダプリルは高血圧を伴うCKD患者において、腎保護的に作用することが確認された。

キーワード：蛋白尿、血圧、イミダプリル（ACE阻害薬）、CKD、日本—インドネシア