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研究成果の刊行物・別刷

腎臓病総合レジストリー

横　山　仁

別　刷
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腎臓病総合レジストリー

横山　仁

それまで，わが国の公的機関による腎臓病登録は行われていなかったが，日本腎臓学会は，2007年よりUniversity Hospital Medical Information Network（UMIN）を活用した腎生検登録データベース（Japan Renal Biopsy Registry；J-RBR）を開始した．さらに，これを基礎に2009年より難治性ネフローゼ症候群，急速進行性腎炎症候群，多発性嚢胞腎（PKD）等を含んだ非腎生検例も登録可能とした腎臓病総合レジストリー（Japan Kidney Disease Registry；J-KDR）へと発展させた．

1. J-RBRの登録状況

症例ごとに実施施設名，病理診断施設名，臨床診断，病理組織診断，年齢，性別，身長，体重，尿検査所見，血液検査・腎機能検査所見（血清クレアチニン，総蛋白，アルブミン，コレステロール）をWeb上で登録し，2009年9月末で4,612例が登録された．そのうち2007年の818例（男性430例，女性388例）における移植腎生検を除いた726例の臨床診断の内訳は，慢性腎炎症候群53.4%，ネフローゼ症候群19.0%，持続性血尿症候群5.6%，膠原病もしくは血管炎症候群5.6%，急速進行性腎炎症候群4.5%，代謝性疾患4.0%，急性腎炎症候群2.0%であった．病理組織学的にはIgA腎症が32.9%と最も多く，次いで原発性（一次性）糸球体疾患が26.3%を占め，なかでも膜性腎症が8.3%であった．

Data Base for Renal Diseases in Japan
Hitoshi Yokoyama：Division of Nephrology, Kanazawa Medical University
金沢医科大学医学部教授（腎機能治療学），日本腎臓学会腎臓病総合レジストリー小委員会委員長

2. J-KDRの構築

先にも述べたように，J-RBRは腎生検実施例のみを登録したが，厚生労働科学研究費補助金難治性疾患克服事業「進行性腎障害に関する調査研究」班（以下，進行性腎障害調査研究班）において重点疾患とされているIgA腎症，急速進行性腎炎症候群，難治性ネフローゼ症候群，多発性嚢胞腎では，診断に腎生検が必須のIgA腎症を除いて臨床的判断により腎生検を実施していない症例が少なからず存在する．そこで，非腎生検例も登録し，重点研究課題7疾患［難治性ネフローゼ症候群，急速進行性糸球体腎炎症候群（RPGN），IgA腎症，多発性嚢胞腎，血管炎症候群，慢性腎臓病（CKD），小児腎臓病］を中心とした臨床情報収集により，わが国における腎臓病の実際を把握するとともに，これら疾病に対する研究推進を行う目的でJ-KDRが構築された．登録内容は，病理所見を除いてJ-RBRと共通項目となっているが，2009年1月より血圧（収縮期，拡張期），降圧薬の服用，HbA1c，糖尿病診断の有無の追記が可能となった．

3. J-RBR/J-KDRの臨床・疫学・病理研究への応用

日本腎臓学会および進行性腎障害調査研究班における二次研究の具体例として，進行性腎障害調査研究班による，ネフローゼ症候群の前向き疫学研究，Japan Nephrotic Syndrome Cohort Study（JNSCS）研究など，2009年9月末で5研究課題が開始されている．

以上，現在進行している日本腎臓学会と進行性腎障害調査研究班による，腎臓病総合レジストリーの概要と状況について述べた．このレジストリーにより，わが国における腎臓病の実態把握と臨床・疫学・病理研究の推進が期待される．

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Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan): Rationale and study design

Kenichi Shikata [a], *Masakazu Haneda* [b], *Daisuke Koya* [c], *Yoshiki Suzuki* [d], *Yasuhiko Tomino* [e], *Kenichi Yamada* [f], *Shiro Maeda* [g], *Norito Kawakami* [h], *Takashi Uzu* [i], *Motonobu Nishimura* [j], *Chikage Sato* [a], *Daisuke Ogawa* [a], *Hirofumi Makino* [a,*]

DNETT-Japan Study Group

[a] *Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[b] *Department of Medicine, Division of Metabolism and Biosystemic Science, Asahikawa Medical College, Asahikawa, Japan*
[c] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Kanazawa Medical University, Ishikawa, Japan*
[d] *Health Administration Center, Niigata University, Niigata, Japan*
[e] *Division of Nephrology, Department of Internal Medicine, Juntendo University School of Medicine, Tokyo, Japan*
[f] *Metabolic Diseases Clinic, Chiba, Japan*
[g] *Laboratory for Endocrinology and Metabolism, RIKEN Center for Genomic Medicine, Yokohama, Japan*
[h] *Department of Mental Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan*
[i] *Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan*
[j] *Department of Internal Medicine, Japan National Hospital Organization Chiba-East National Hospital, Chiba, Japan*

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ABSTRACT

The prevalence of end-stage renal disease (ESRD) is uprising in the paralleled with the increase of chronic kidney disease (CKD) patients. Diabetic nephropathy (DN) is the most important underlying disease of CKD and a leading cause of ESRD in Japan. Intensified multifactorial intervention in patients with type 2 diabetes with microalbuminuria slows the progression to nephropathy, and progression of retinopathy and autonomic neuropathy. However, further studies are needed to establish the effect of intensified multifactorial treatment on DN with overt proteinuria. In this trial, doctors and co-medicals collaborate to treat the DN patients to prevent the deterioration of DN by multifactorial intensive therapy. Diabetic Nephropathy Remission and Regression Team Trial in Japan (DNETT-Japan) is an open, randomized controlled trial to evaluate the efficacy of renal protection of multifactorial intensive therapy in type 2 diabetes patients with overt proteinuria (urinary albumin-to-creatinine ratio ≥300 mg/g creatinine). The study has a targeted enrollment of 600 Japanese patients, and divided into two protocols by renal insufficiency (protocol A: serum creatinine: <1.2 mg/dl in male and <1.0 mg/dl in female, and protocol B: serum creatinine: 1.2–2.5 mg/dl in male and 1.0–2.5 mg/dl in female). The patients were allocated standard treatment or intensive multifactorial treatment. Intensive treatment was a stepwise implementation of behavior modification, pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia, and proteinuria. The primary outcome is the

* *Corresponding author at*: Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan. Tel.: +81 86 235 7235; fax: +81 86 222 5214.
E-mail address: makino@md.okayama-u.ac.jp (H. Makino).
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proteinuria in protocol A and the composite endpoint of time to the first occurrence of doubling of serum creatinine, ESRD (the need for chronic dialysis, or renal transplantation) or death in protocol B. The follow-up period is 5 years and the study ends in 2014.

1. Introduction

Diabetic nephropathy (DN), one of the major complications of diabetes mellitus, is the leading cause of end-stage renal disease (ESRD) and about 43% of the patients newly introduced to chronic dialysis therapy are due to DN in Japan [1]. More than 275,000 HD are under chronic dialysis, and the number of the patients newly introduced to chronic dialysis is still increasing [1]. In line with the growing concerns about escalating medical costs and the increased risk of cardiovascular disease caused by chronic kidney disease (CKD) [2], the effective intervention in the development of DN and the progression of ESRD has been urgently required.

It is critical to manage blood glucose, hypertension and proteinuria aggressively to interrupt the development of DN [3]. In recent studies, strict blood glucose and blood pressure control using renin-angiotensin system (RAS) inhibitors has been confirmed to reduce the progression of DN. Although it is not sufficient to reduce the increasing numbers of ESRD patients, Steno 2 trial conducted in type 2 diabetic patients with microalbuminuria has shown that multifactorial approach can slow the progression of microvascular complications including DN [4,5]. This trial showed that the progression of DN is modifiable by multifactorial intervention. Furthermore, it is reported that strict management of hyperglycemia and hypertension with RAS inhibitors can lead to the remission and regression of DN [6]. However, these studies were performed at a single institution and the scale of the studies is relatively small, and so far, there is no evidence that intensive multifactorial therapy can inhibit the progression of DN with overt proteinuria.

In order to examine the effect of intensive multifactorial intervention on the inhibition of progression of DN with overt proteinuria, we are conducting a large-scale clinical trial named DNETT-Japan (Diabetic Nephropathy Remission and Regression Team Trial in Japan). This trial is a randomized, open labeled, multi-centered study to investigate whether intensive multifactorial intervention that includes changes in behavior and pharmacological therapy can conduct the remission and regression of DN in type 2 diabetic patients with overt proteinuria compared with a standard treatment.

2. Methods

2.1. Patients

The DNETT-Japan is a multi-center study currently underway in Japan (Clinical Trials gov number, NCT00253786). Japanese patients with type 2 DN met the inclusion and exclusion criteria have been shown in Table 1 and have been enrolled. The trial is being conducted under the Helsinki Declaration, and was approved by the Institutional Review Board at each trial site. All participants have been fully informed by the investigators and gave their written informed consent.

2.2. Study design

This clinical trial is a randomized, open labeled, multi-center study (Fig. 1). During the 2-month screening period (already completed), patients were assessed for inclusion and exclusion criteria for eligibility for entering this study. The active treatment period is 5 years. Patients are randomly assigned standard treatment or intensive multifactorial treatment with behavior modification and stepwise introduction of pharmacological therapy (Table 2).

The study is a randomized, open, parallel trial. Patients are randomly assigned standard treatment or intensive multifactorial intervention with behavior modification and stepwise introduction of pharmacological therapy (Table 2). The stepwise approach was chosen to maximize compliance to the protocol. Standard treatment is performed according to the guideline of the Japanese Diabetes Society, Japanese Society of Hypertension, and Japanese Atherosclerosis Society. Patients in the intensive group are treated by a project team (doctor, nurse, dietician and pharmacologist) at each institution. The aim of dietary intervention is a total intake of protein less than 0.8 g/kg/day, and intake of sodium less than 5 g/day, and total daily energy intake less than 30 kcal/kg/day. Hemoglobin A1c (HbA1c) values should be below 5.8% on diet alone, and if patients are unable to maintain HbA1c < 5.8%, oral hypoglycemic agents or insulin is started. The target blood pressure

Table 1 – Eligibility criteria.

Inclusion criteria
(1) Patients with type 2 diabetes
(2) Urinary albumin-to-creatinine ratio: ≥300 mg/g creatinine twice in the first morning urine sample
(3) Serum creatinine level: ≤2.5 mg/dl
(4) Patients aged 20–75 years

Exclusion criteria
(1) Type 1 diabetes
(2) Hereditary diabetes or secondary diabetes
(3) Non-diabetic nephropathy
(4) Familial hypercholesterolemia
(5) Secondary hypertension
(6) Unstable angina pectoris or history of myocardial infarction/stroke within 6 months prior to consent acquisition
(7) Malignant tumor or life threatening disease
(8) History of angioedema
(9) Patients undergoing LDL apheresis
(10) Billiary system obstruction or severe liver injury
(11) Liver dysfunction
(12) Allergy for ACE-Is, ARBs or HMG-CoA reductase inhibitors
(13) Pregnant or nursing patients
(14) Others: patients who are not suitable for this trial

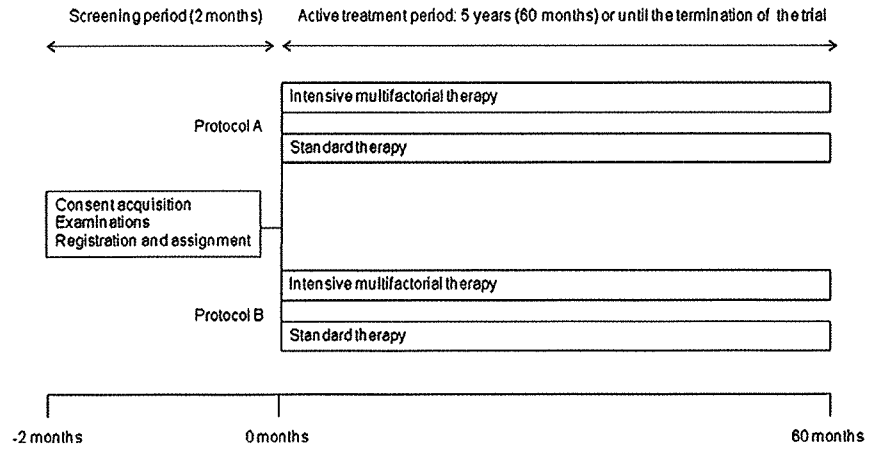

Fig. 1 – Overview of the design of DNETT-Japan.

should be <125 mmHg systolic blood pressure and <75 mmHg diastolic blood pressure (seated blood pressure) in intensive therapy group using angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACE-Is) for the management of hypertension. If the target blood pressure of less than 125/75 mmHg is not achieved, both ARBs and ACE-Is are used concomitantly. Even if the target blood pressure levels are not achieved in a patient with ARBs and ACE-Is, long acting calcium channel blockers are used. HMG-CoA reductase should be used for the reduction of LDL-cholesterol levels less than 100 mg/dl. All patients who smoke and their spouses are invited to smoking cessation courses. All patients received multivitamin supplement daily.

All patients will visit the clinic at every 3 months throughout the study duration. At each visit, blood pressure will be measured and clinical samples collected for the measurement of the urinary protein-to-creatinine ratio, and the levels of serum creatinine and serum potassium. Glomerular filtration rate (GFR) is estimated using the following modified MDRD formula for Japanese participants: GFR (ml min^{-1} 1.73 m^{-2}) = 194 × [serum creatinine (μmol/l)]$^{-1.094}$ × [age (years)]$^{-0.287}$ × (0.739 if female) [7]. All randomized patients including those discontinued from the study for any reason other than death will be followed up to collect information on primary and secondary endpoints until termination of study.

2.3. *Study endpoints*

The primary and secondary endpoints are shown in Table 3. The primary endpoint is a proteinuria in protocol A, and a composite endpoint of the time to first occurrence of doubling of serum creatinine, ESRD, or death in protocol B. ESRD is defined as the need for chronic dialysis or renal transplantation. The secondary endpoints are GFR, cardiovascular event, progression of retinopathy, urinary albumin/creatinine ratio,

Table 2 – Treatment goals and interventions for standard and intensive multifactorial groups.

	Intensive multifactorial	Standard
Blood glucose	HbA1c < 5.8%	HbA1c < 6.5%
Blood pressure	SBP < 125 mmHg DBP < 75 mmHg	SBP < 130 mmHg DBP < 80 mmHg
Lipid profile	T-cho < 180 mg/dl LDL-cho < 100 mg/dl HDL-cho >40 mg/dl	T-cho < 200 mg/dl LDL-cho < 120 mg/dl HDL-cho >40 mg/dl
Dietary intervention	TDEI < 30 kcal/kg/day Sodium < 5 g/day Protein < 0.8 g/kg/day	TDEI 25-30 kcal/kg/day Sodium < 6 g/day Protein < 1.0 g/kg/day
Pharmacological intervention	ACE-Is or ARBs HMG-CoA reductase inhibitors Muitivitamins	No restrictions (continuing prior therapy)
Instruction by co-medicals	Taking medicines Smoking cessation Nutrition care	No restrictions (continuing prior therapy)

SBP, systolic blood pressure; DBP, diastolic blood pressure; T-cho, total cholesterol; LDL-cho, LDL-cholesterol; HDL-cho, HDL-cholesterol; TDEI, total daily energy intake.

Table 3 – Primary and secondary endpoints.

Protocol A
Primary outcomes
Urinary protein/creatinine ratio (in the first morning urine sample)
Secondary outcomes
(1) GFR
(2) Cardiovascular event
(3) Progression of retinopathy
(4) Urinary albumin/creatinine ratio
(5) Proteinuria (24 h collection sample)
Protocol B
Primary outcomes
Composite endpoint of time to first occurrence of
(1) Doubling of serum creatinine
(2) Need for chronic dialysis or renal transplantation
(3) Death
Secondary outcomes
(1) GFR
(2) Cardiovascular event
(3) Progression of retinopathy
(4) Urinary albumin/creatinine ratio
(5) Urinary protein/creatinine ratio

and proteinuria in protocol A and GFR, cardiovascular event, progression of retinopathy, urinary albumin/creatinine ratio, and protein/creatinine ratio in protocol B.

2.4. *Statistical analysis*

The primary efficacy analysis set will be the full analysis set (FAS). The FAS will include all patients satisfying the following conditions: (1) fulfilled all entry criteria; (2) assigned randomly; (3) were followed up with intensive or standard treatment; (4) were evaluated at least once after randomization. The secondary efficacy analysis set will be per protocol set (PPS). The PPS will consist of patients included in the FAS who had no major protocol violations.

The Cox regression model will be used to estimate the hazard ratios with 95% confidence intervals in the renal composite event rate, the cerebro/cardiovascular composite event rate, and the event rate for each renal, cerebro- or cardiovascular event separately. The covariates included in the model will be determined based on the results of blind data review before the study is unblinded. The candidate covariates are gender, age, ACE-I treatment, baseline urinary albumin:-creatinine ratio and baseline serum creatinine level. The cumulative event rate for each defined event will be estimated by the Kaplan–Meier's method for each treatment group. The linear mixed effect model, including study drugs, measurement times and other covariates selected after the blind data review, will be used for comparing the trend in the percent change in proteinuria, and the trend in the reciprocal of the serum creatinine level between treatment groups. Similar analyses for each endpoint will also be applied for the subgroup of each prognostic factor.

Adverse events will be summarized for each treatment group. The cumulative occurrence rate of all adverse events and drug-related adverse events in each treatment group will be estimated by the Kaplan–Meier's method, and the log-rank test will be used to compare two groups. The summary statistics, such as the mean, median and standard deviation for the quantified laboratory test values, will be calculated at each measurement point, and scatter plots of each of the test values for pre- and post-treatment will be presented. Contingency tables showing the number of patients and the percentage of patients within each category pre- and post-treatment will also be presented for the categorical test values.

3. Discussion

The purpose of DNETT-Japan is to investigate that intensive multifactorial treatment may attenuate the progression of DN in patients with type 2 diabetes and overt proteinuria in the Japanese populations. DN is a leading cause of ESRD in Japan, and the HD patients are still increasing based on the epidemic of type 2 diabetic patients. DN is also the most popular CKD, and recently it is well recognized that CKD is a high risk factor for cardiovascular disease (CVD) and stroke. In consideration for the rising burden of ESRD and CVD, there is a need to establish the treatment for DN in Japanese diabetic patients.

Strict control of blood glucose and blood pressure is principal in the treatment of DN. Intensive glucose control had a beneficial effect on aggregate diabetes-related endpoints and significantly reduced the rate of progression from normoalbuminuria to microalbuminuria in the United Kingdom Prospective Diabetes Study [8]. However, there is no significant reduction in the risk of progression of DN; intensive blood glucose control alone seems insufficient to treat diabetic patients with overt proteinuria. Moreover, recent study reported that intensive glucose lowering therapy increased the mortality and did not reduce the cardiovascular events in type 2 diabetic patients [9]. Although intensive insulin therapy had the effect on progression to proteinuria [10], there is no evidence that strict control of blood glucose solely prevents the progression of DN with overt proteinuria.

In order to interrupt the development of DN, it is critical to manage not only blood glucose, but also hypertension. ACE-Is or ARBs are recommended as first-line drugs in the treatment of hypertension according to the American Diabetes Association (ADA) Position Statement [11] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [12]. Both classes of drugs reduced the risks of onset of DN, increase in proteinuria and progression to ESRD [13]. ARBs are recommended especially for DN in type 2 diabetes, based on the evidence of large-scale randomized controlled trials in DN [14–17]. In recent years, large-scale clinical trials conducted in type 2 diabetic patients with microalbuminuria, such as the INNOVATION of telmisartan [14] and the IRMA-2 of irbesartan [15], have shown that angiotensin II receptor blockers (ARBs) can prevent the progression of microalbuminuria to overt proteinuria. The clinical trials of DN with proteinuria, such as the RENAAL study of losartan [16], the IDNT study of irbesartan [17], have demonstrated that the treatment with ARBs can significantly reduce the risk of doubling of the serum creatinine level, dialysis, renal transplantation, and death.

When the protocol for DNETT-Japan was designed in 2005, the recommended target blood pressure according to the

hypertension treatment guidelines in Japan (JSH 2004) was <125/75 mmHg. If blood pressure is above 125/75 mmHg, we recommend to use both ACE-I and ARB in this trial. A combination therapy with an ACE-I and ARB has been suggested to exert stronger anti-proteinuric effects than either agent used alone [3], and this combination effect of an ACE-I and ARB on proteinuria has been examined in DN patients [18]. We will evaluate the effect of strong inhibition of rennin-angiotensin system in addition to the tight control of blood pressure on the progression of DN.

Intensified multifactorial intervention improved the progression of DN and the mortality in patients with microalbuminuria in Steno 2 study [4,5,19]. This study pointed out that multifactorial approach, not only the treatment for hyperglycemia and hypertension but also dyslipidaemia and other pharmacological therapy using vitamins and aspirin, is beneficial for the progression from microalbuminuria to overt proteinuria. However, thus far, there is no evidence that intensive multifactorial therapy can reduce the progression of DN with overt proteinuria. Thus, we designed this trial to clarify the effect of intensive multifactorial intervention on remission and regression of DN, and to establish the treatment of DN by medical team with doctors and co-medicals.

In conclusion, DNETT-Japan aims to investigate the efficacy of intensive multifactorial therapy in Japanese type 2 diabetic patients with DN. Results from this trial are expected to provide further evidence regarding the treatment strategy in patients with overt proteinuria.

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Conflict of interest

There are no conflicts of interest.

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DATA UPDATE CARDIOVASCULAR 4th EDITION

Supervisor:
Satoshi Ogawa

Editors:
Masahiko Kurabayashi
Issei Komuro
Hiromi Rakugi

SENTAN IGAKU-SHA

INNOVATION

●Incipient to Overt：Angiotensin Ⅱ Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy

❶ 対象疾患

糖尿病性腎症（早期）.

❷ 目　的

2型糖尿病性腎症症例においてARBテルミサルタンが早期腎症から顕性腎症への移行を抑制するか否かを検討する.

❸ 対象症例

30～74歳の2型糖尿病と診断され，早朝第一尿中アルブミン排泄率が100～300 mg/g·Crの微量アルブミン尿を呈し，血清Cr値が男性で1.5 mg/dl未満，女性で1.3 mg/dl未満の正常血圧症例および高血圧症例，計527例.

❹ 方　法

・被験者をテルミサルタン80 mg群，40 mg群，プラセボ群の3群に無作為に割り付け，二重盲検法により平均1.3年間観察した.
・一次エンドポイントは微量アルブミン尿から顕性腎症（尿中アルブミン排泄率300 mg/g·Cr以上かつベースライン値からの30%以上の上昇）への移行，二次エンドポイントは微量アルブミン尿の正常化（尿中アルブミン排泄率30 mg/g·Cr未満）とした.

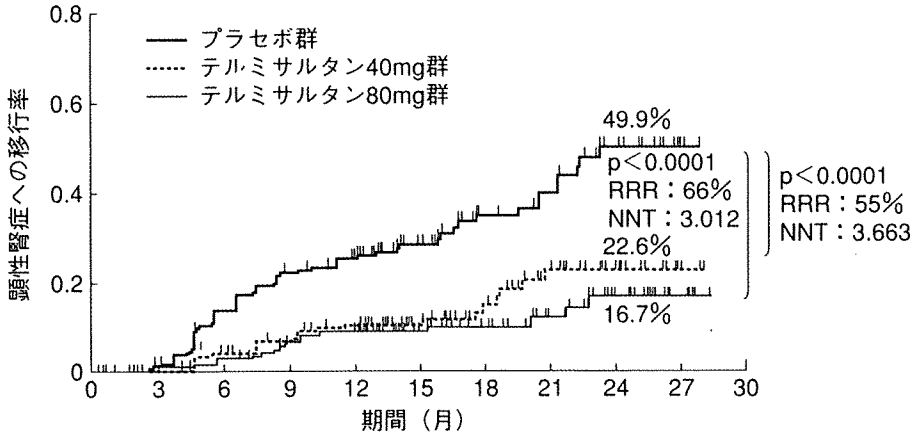
❺ 結　果

治療期間中の顕性腎症への移行率は，テルミサルタン80 mg群16.7%，40 mg群22.6%，プラセボ群49.9%と，テルミサルタン群では用量の異なる2群ともに顕性腎症への移行が有意に抑制された（**図❶**）．治療必要数（NNT）は，テルミサルタン80 mg群では3.0例，40 mg群では3.7例であり，微量アルブミン尿を伴う2型糖尿病性腎症症例3～4例にテルミサルタンを投与すると，顕性腎症への移行を1例減らすことができることが示された．尿中アルブミン排泄率は，テルミサルタン80 mg群では58.8 mg/g·Cr，40 mg群では37.9 mg/g·Cr低下し，プラセボ群では40.9 mg/g·Cr上昇した．また，微量アルブミン尿の正常化率は，テルミサルタン80 mg群21.2%，40 mg群12.8%，プラセボ群1.2%と，テルミサルタン群において有意に高く，顕性腎症への移行抑制効果とともに，明らかな腎保護効果を認めた.

また，本試験は正常血圧症例（163例）も対象としており，治療期間中の顕性腎症への移行率は，テルミサルタン80 mg群11.0%，40 mg群21.0%，プラセボ群44.2%と，テルミサルタン群では用量の異なる2群ともに顕性腎症への移行が有意に抑制された（**図❷**）．このことより，高血圧症例と同様に正常血圧症例においてもテルミサルタンが顕性腎症への移行を有意に抑制することが示された．さらに微量アルブミン尿の正常化率も，テルミサルタン80 mg群19.6%，40 mg群15.5%，プラセボ群1.9%とテルミサルタン群で有意に高く，顕性腎症への移行抑制とともに明らかな腎保護作用を認めた.

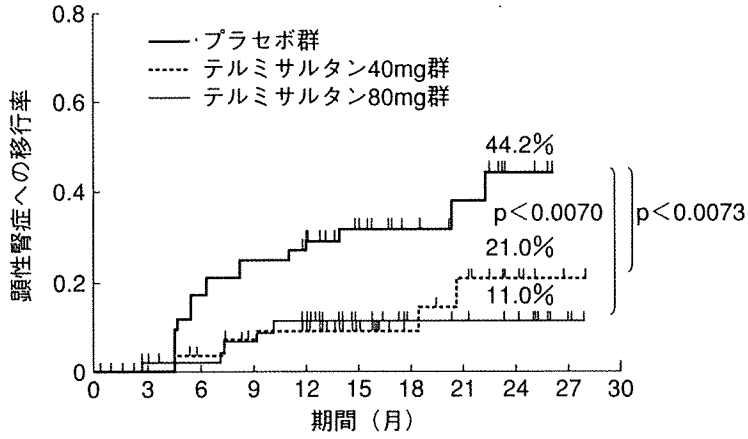
❻ コメント・評価

海外においてロサルタンやイルベサルタンなどのARBが糖尿病性腎症の進展を抑制すると報告され，わが国においても糖尿病性腎症の治療として厳格な血糖コントロールだけでなく，レニン・アンジオテンシン（RA）系抑制薬を基本とした厳格な降圧療法が推奨されている．最近までわが国における糖尿病性腎症に対するARBのエビデンスはなかったが，本試験においてはじめて日本人



図❶ 顕性腎症への移行率

（Makino H *et al*, 2007[1]より引用）



図❷ 正常血圧症例における顕性腎症への移行率

（Makino H *et al*, 2007[1]より引用）

の2型糖尿病性腎症症例を対象とし，テルミサルタンが早期腎症から顕性腎症への移行を抑制することが示された．

（小川大輔/槇野博史）

❖

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高血圧 下

—日本における最新の研究動向—

臨床編

XII　日本人の大規模臨床試験

INNOVATION

小川大輔　　槇野博史

XII. 日本人の大規模臨床試験

INNOVATION

小川大輔[1]　槇野博史[2]

Key words：大規模臨床試験，高血圧，糖尿病性腎症，微量アルブミン尿，アンジオテンシンII受容体拮抗薬(ARB)

はじめに

2009年1月に日本高血圧学会より‘高血圧治療ガイドライン2009’が発表された．今回の新しいガイドラインの主な変更点の一つは，糖尿病を合併する高血圧の治療において，第一選択薬からカルシウム拮抗薬が除かれ，アンジオテンシン変換酵素(ACE)阻害薬あるいはアンジオテンシンII受容体拮抗薬(ARB)となったことである[1]．以前より欧米で実施された高血圧を合併した糖尿病性腎症の臨床研究により，ACE阻害薬やARBによるタンパク尿増加や腎機能低下を抑制する効果が報告されており，我が国においてもレニン・アンジオテンシン系(RAS)抑制薬を基本とした厳格な降圧療法が推奨されていた．ただ，最近まで日本人の糖尿病性腎症患者を対象としたARBのエビデンスはなかったが，我が国において実施されたINNOVATION (Incipient to Overt: Angiotensin II Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy)試験により，我が国においても糖尿病性腎症に対するARBの有用性が明らかにされた[2]．そしてこのINNOVATION試験は，今回の高血圧治療ガイドラインの改定において，糖尿病を合併する高血圧の治療の第一選択薬はカルシウム拮抗薬ではなくRAS抑制薬となったことに寄与した重要な試験である．

本稿では，初めて日本人の2型糖尿病性腎症患者を対象とし，ARBの早期腎症から顕性腎症への進展抑制を検討した試験であるINNOVATIONについて概説する．

1. INNOVATIONの試験方法

a. 目　的

2型糖尿病に伴う微量アルブミン尿を呈する日本人の糖尿病性腎症患者に対するARBテルミサルタンの顕性腎症への移行抑制効果と安全性を，プラセボを対照として比較検討することである．

b. 対象症例

30-74歳の2型糖尿病と診断された者で，早朝第一尿中のアルブミン排泄率が100-300 mg/g・Crの微量アルブミン尿を呈し，血清クレアチニン値が男性で1.5 mg/dL未満，女性で1.3 mg/dL未満の正常血圧患者および高血圧患者，計527例を対象とした．

c. 評価項目(エンドポイント)

主要評価項目は微量アルブミン尿から顕性腎症(尿中アルブミン排泄率300 mg/g・Cr以上かつベースライン値からの30％以上の上昇)への移行と定義した．二次評価項目は微量アルブミン尿の正常化率(尿中アルブミン排泄率30 mg/g・Cr未満)とした．

[1]Daisuke Ogawa: Department of Diabetic Nephropathy, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences　岡山大学大学院医歯薬学総合研究科 糖尿病性腎症治療学　[2]Hirofumi Makino: Department of Medicine and Clinical Science　同 腎・免疫・内分泌代謝内科学

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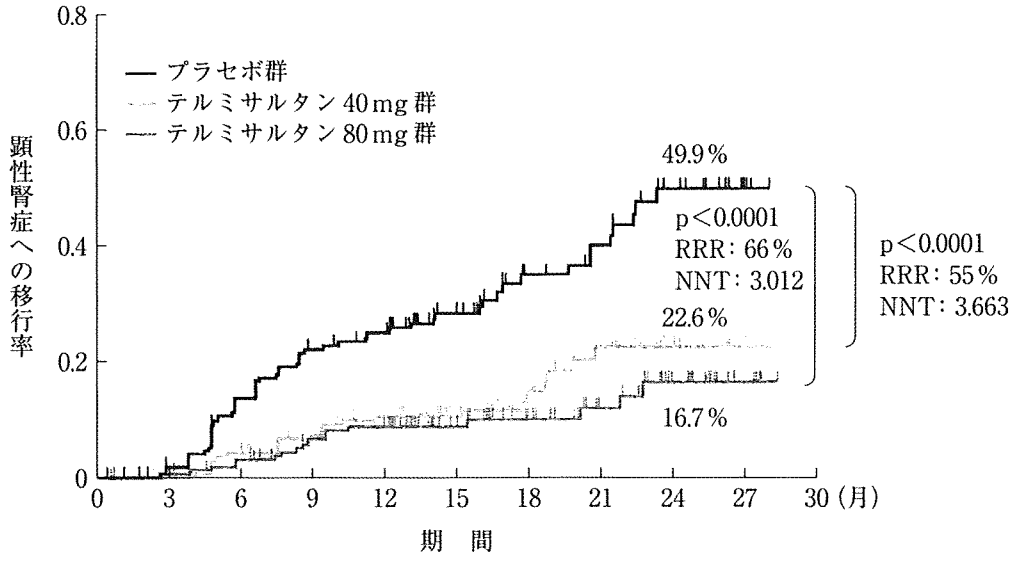
a.



b.

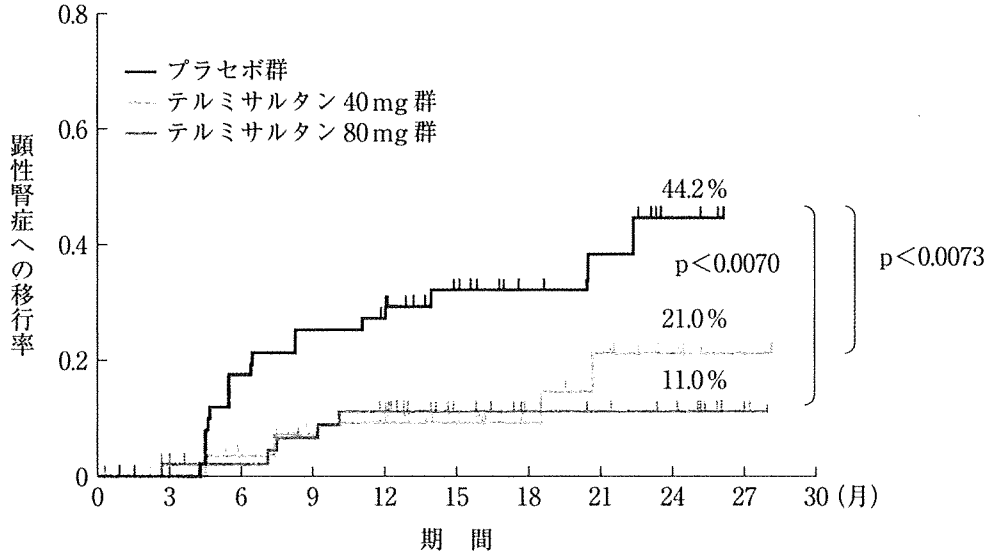


図1 早期腎症から顕性腎症への移行率（a），正常血圧患者における顕性腎症への移行率（b）（文献[2]より引用）
RRR：relative risk reduction，NNT：number needed to treat.

d. プロトコール

本試験は多施設共同，二重盲検，ランダム割付，群間比較試験である．被験者はテルミサルタン80mg群，テルミサルタン40mg群，プラセボ群の3群にランダムに割り付けた．降圧治療目標値は130/85mmHgとし，ARBおよびACE阻害薬を除く降圧薬の併用は可能とした．投与期間は最長124週間とし，平均投与期間は1.3年（最長2.3年）であった．

2. INNOVATIONの主要結果

主要評価項目である顕性腎症への移行率は，テルミサルタン80mg群16.7%，40mg群22.6%，プラセボ群49.9%であり，テルミサルタン群では用量の異なる2群ともに顕性腎症への移行を有意に抑制した（log-rank検定：$p<0.0001$）（**図1-a**）．NNT（number needed to treat）は，テルミサルタン80mg群では3.0人，40mg群では3.7人であり，微量アルブミン尿を伴う2型糖

尿病性腎症患者3-4人にテルミサルタンを投与すると，1人は顕性腎症への移行を抑制できることが示された．また，正常血圧患者のみの解析でも，顕性腎症への移行率はテルミサルタン80 mg群11.0％，40 mg群21.0％，プラセボ群44.2％と，テルミサルタンは2用量ともに顕性腎症への移行を有意に抑制した(**図1-b**)．

二次評価項目である尿中アルブミン排泄率は，観察期ベースラインからテルミサルタン80 mg群では58.8 mg/g・Cr，40 mg群では37.9 mg/g・Cr低下したが，プラセボ群では40.9 mg/g・Cr上昇した(ANCOVA: $p<0.0001$)．また，微量アルブミン尿の正常化率は，テルミサルタン80 mg群21.2％，40 mg群12.8％，プラセボ群1.2％と，テルミサルタン群において有意に高く，顕性腎症への移行抑制とともに明らかな腎保護作用を認めた(Fisher直接確率計算法：$p<0.0001$)．更に，正常血圧患者のみの解析でも，微量アルブミン尿の正常化率は，テルミサルタン80 mg群19.6％，40 mg群15.5％，プラセボ群1.9％とテルミサルタン群で有意に高かった[3]．

以上の結果より，微量アルブミン尿を伴う2型糖尿病患者において，ARBテルミサルタンは顕性腎症への移行を有意に抑制することが示された．また，この効果は高血圧患者のみならず正常血圧患者においても同様に認められた．更に，テルミサルタンは微量アルブミン尿の正常化率も有意に増加させた．

3. INNOVATION試験の意義

糖尿病の細小血管合併症としては腎症や神経障害，網膜症があり，特に糖尿病性腎症が存在すると予後不良であることはよく知られている．一方，糖尿病と高血圧はいずれも動脈硬化による大血管障害の重要な危険因子であるが，両者が合併すると脳血管障害や虚血性心疾患の発症頻度が大きく増加することも周知の事実である．したがって，糖尿病合併高血圧患者においては，細小血管障害や大血管障害を予防し進展を抑えるためにも，厳格な血糖管理とともに，血圧の厳格な管理が重要となる．

糖尿病性腎症の進展抑制を目的としたARBによる介入試験としては，早期腎症患者を対象としたIRMA2[4]やMARVAL[5]，顕性腎症後期から腎不全期の患者を対象としたIDNT[6]やRENAAL[7]がある．いずれの試験においてもARBによる腎症進行の抑制効果が認められている．しかし，これまでに報告されている2型糖尿病患者に対するARBの腎保護作用は，主に欧米人を対象とした検討であり，日本人の糖尿病性腎症患者を対象としたARBによる介入研究の実施が望まれていた．INNOVATIONは，微量アルブミン尿を伴う2型糖尿病患者を対象にARBの効果を検証する試験として，日本人を対象にした初めての大規模臨床試験であり，日本オリジナルのARBのエビデンスとして極めて重要な試験である．

INNOVATIONにおいて，テルミサルタンは顕性腎症への進展を抑制し，更に微量アルブミン尿の正常化率も有意に増加させた．これは早期腎症からテルミサルタンで治療すれば，顕性腎症への移行，ひいては末期腎不全への移行を抑制できることを示唆する成績であり，早期からのARBによる治療の重要性を示すものである．また10-20％の患者で微量アルブミン尿が正常化することから，糖尿病性腎症の退縮や寛解にも期待がもてる結果である．更に，テルミサルタンの顕性腎症への進展抑制効果は，高血圧患者のみならず，正常血圧患者においても同様に認められ，高血圧を伴わない糖尿病性腎症患者に対してもテルミサルタンを投与することで腎保護作用が期待できることを示している．

2000年以降に発表された疫学研究および臨床研究により，微量アルブミン尿を認める段階から心血管疾患死のリスクが高くなることが明らかとなった[8-10]．この点を踏まえると，INNOVATIONで得られたテルミサルタンの腎保護作用は，ARBによる糖尿病性腎症の進展抑制効果のみならず，2型糖尿病における心血管合併症の発症予防効果をも示唆するものである．高血圧を合併する糖尿病性腎症患者においては，心血管イベントを予防し腎症の進行を抑えるためにも，血糖管理とともにRAS抑制薬をベース

にした厳格な血圧のコントロールが重要である．

おわりに

INNOVATIONは，2型糖尿病性腎症患者を対象に，ARBによる腎保護効果を我が国において初めて実証した大規模臨床試験である．この試験により，日本人においても持続性のタンパク尿が認められる前の微量アルブミン尿の段階から，高用量のテルミサルタンを含む積極的治療を行うことにより腎症の進行を抑制し，一部の症例においては正常化することが明らかになった．今後，糖尿病を合併する高血圧患者の治療において，顕性腎症への移行および心血管合併症の発症を予防することが期待される．

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ORIGINAL ARTICLE

Physicians make different decisions from nephrologists at serum creatinine 2.0 mg/dl

Kaichiro Tamba · Eiji Kusano · Kaoru Tabei · Eiji Kajii · Yasushi Asano

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Abstract
Background It is very important, but not clear, how physicians differ from nephrologists in treatment of renal insufficiency.
Aim To demonstrate differences in decision-making in treatment of renal insufficiency between physicians and nephrologists.
Design of study Postal questionnaire.
Setting All physicians were graduates from one medical school and certified by the Japanese Society of Internal Medicine. Nephrologists were certified by the Society and the Japanese Society of Nephrology.
Method Questionnaires were sent to 1,395 physicians and 385 nephrologists, including audit of serum creatinine concentration that would indicate referral to nephrologist, audit of continuation of angiotensin converting enzyme inhibitor (ACEI) for a case of renal insufficiency and mild hyperkalemia due to ACEI. Outputs were proportion that selected "serum creatinine 177 μmol/l (2.0 mg/dl) and over" as a referral point to the nephrologist, and proportion that chose "suspend ACEI" for a case of renal insufficiency and mild hyperkalemia due to ACEI.
Results Six hundred and fourteen physicians replied (44%), and 111 certified in internal medicine were extracted from them. One hundred and eighty-six certified nephrologists replied (47%), and 114 certified in internal medicine were extracted. The proportion that chose "177 μmol/l" as a referral point to the nephrologist was 20% for physicians and 61% for nephrologists ($P < 0.0001$). An additional 17% of nephrologists recommended creatinine concentration below 177 μmol/l, whereas no such opinion was found among physicians. The proportion that chose "suspend ACEI" was 45% for physicians and 16% for nephrologists ($P < 0.0001$).
Conclusion There is significant difference between decisions made by physicians and nephrologists regarding treatment for patients with serum creatinine concentration of 177 μmol/l.

Keywords General physician · Nephrologist · Serum creatinine · Chronic kidney failure

K. Tamba (✉) · E. Kajii
Department of General Practice, School of Medicine, Jichi Medical University, 3111-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
e-mail: kaitamba@jichi.ac.jp

E. Kusano · Y. Asano
Division of Nephrology, Department of Internal Medicine, School of Medicine, Jichi Medical University, 3111-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

K. Tabei
Jichi Medical University Saitama Medical Center, 1-847 Amanuma, Ohmiya-Ku, Saitama 330-8503, Japan

Introduction

The number of patients who undergo renal replacement therapy is increasing at the rate of approximately 10,000 persons per year in Japan. The number of chronically dialyzed patients was about 275,242 at the end of 2007 [1]. This has become a serious medico-economical problem because the total annual costs for dialysis therapy exceeded US $14 billion (¥1.3 trillion) in 2004.

Recently, early referral to nephrologist was recommended in several papers [2–4]. The guidelines of the National Kidney Foundation recommended that glomerular

filtration rate (GFR) below 30 ml/min/1.73 m^2 should be referred to nephrologist [5]. However, it is still unclear when is the best time.

It is evident that proper use of ACEI, and strict control of blood pressure and blood glucose, can delay or prevent progression of renal dysfunction [6–8]. However, most Japanese physicians do not seem to be competent at treating renal diseases. They have less chance and experience of seeing renal patients than do nephrologists. Moreover, progression of chronic kidney diseases is very slow. It takes years for the severity of the disease to manifest itself, at which point it is already too late. This means that most physicians may overlook the importance of maintaining kidney function. If physicians referred patients to nephrologists at the appropriate stage of renal dysfunction, the number of Japanese end-stage renal disease (ESRD) patients would not increase at such an alarming rate.

We surveyed the differences in decisions made in treatment of renal insufficiency between physicians and nephrologists in Japan, and found that there is a wide gap between them. We draw attention to the possibility of a similar rift between physicians and nephrologists in other countries.

Method

This study is based on the results of a posted, anonymous, self-administered survey. We sent the survey in December 2003 and January 2004. Background data about physicians were collected on gender, career, specialty, workplace, final training in nephrology, numbers of daily renal patients, renal tests used for outpatients and access to nephrologist and dialysis machine. The survey included multiple-choice and/or multiple-select questions about renal diseases and specific cases.

Questionnaires were sent to 1,395 physicians and 385 nephrologists authorized by the Japanese Society for Nephrology. The nephrologists were extracted by random-number selection from a list of certified nephrologists on the homepage of the Japanese Society for Nephrology. Physicians were extracted from the address book of the graduates of Jichi Medical School. Jichi Medical School was established in 1972 to ensure and improve the level of medical services in remote areas where medical resources are scarce. We extracted those certified by the Japanese Society for Internal Medicine from both nephrologists and physicians. We excluded nephrologists who had been working for more than 27 years in order to match years of work in the two groups, since there were no graduates of Jichi Medical School who had worked for more than 27 years at the time of this survey. We also excluded the physicians who subspecialize in nephrology and those who do not currently see renal patients.

In this study, we analyzed data obtained for the following two questions about mild renal insufficiency, shown below.

Q1. Which is your most preferable concentration of serum creatinine or condition for referral to the nephrologist?

a. 177 μmol/l (2.0 mg/dl)
b. 354 μmol/l (4.0 mg/dl)
c. 530 μmol/l (6.0 mg/dl)
d. 707 μmol/l (8.0 mg/dl)
e. 884 μmol/l (10.0 mg/dl)
f. Uremia
g. Other

Q2. Case of mild renal insufficiency

Fifty-year-old female with a 15-year history of diabetes mellitus. She had proteinuria and her serum creatinine was 177 μmol/l and her serum K was 4.7 mEq/l. You prescribed ACEI because her blood pressure was 150/90 mmHg. One month later, her serum creatinine was 195 μmol/l and her serum K was 5.5 mEq/l. What will you do?

a. Suspend ACEI and prescribe other antihypertensive drugs
b. Do not suspend ACEI and prescribe resin. Advise K restriction
c. Other

Ethical considerations and statistical analysis

We sent a letter of intent that explained the importance of the survey and assured that we would publicize the results. We did not think that this study had ethical problems because it did not include any real patient data and all data were anonymous.

Differences in categorical data were analyzed with χ^2 test. For continuous data, means were compared by unpaired t tests. Means and standard deviations are shown when appropriate.

Results

Postal questionnaire to physicians and nephrologists

Six hundred and fourteen physicians replied (44%), and 111 certified in internal medicine were extracted from

them. One hundred and eighty-six certified nephrologists replied (47%), and 114 certified in internal medicine were extracted. According to the exclusion criteria, 25 physicians and 22 nephrologists were excluded. Characteristics of both groups are shown in Table 1.

Audit of serum creatinine that would indicate referral to nephrologist

Those who chose "177 μmol/l" as a referral point to nephrologists were 22 physicians (19.8%) and 69 nephrologists (60.5%) ($P < 0.001$). An additional 20 nephrologists (17.5%) selected "Other" and recommended a creatinine concentration below 177 μmol/l. No physicians selected "Other" with such comment. This means 89 nephrologists (78.1%) chose 177 μmol/l or below, whereas less than 20% of physicians did (Fig. 1).

Audit of continuance of ACEI in the treatment of a case of renal insufficiency

The responders who chose "Suspend ACEI" were 55 physicians (49.5%) and 18 nephrologists (15.8%) ($P < 0.001$). The responders who chose "Do not suspend ACEI and prescribe resin. Advise K restriction" were 43 physicians (38.7%) and 74 nephrologists (64.9%) ($P < 0.001$). One physician (0.9%) and ten nephrologists (8.8%) chose "Other" and suggested "K restriction only". Five physicians (4.5%) and four nephrologists (3.5%) chose "Other" and suggested "observation for several weeks". Three physicians (2.7%) and three nephrologists (2.6%) chose "Other" and suggested "Reduce ACEI" (Fig. 2).

Discussion

As we all know, physicians are different from specialists in skill, knowledge and experience in a specialty. There may be no problem if differences between physicians and specialists are limited to a very specialized area, but serious problems would arise if there were differences between basic views held by physicians and specialists. However, there has been very little investigation of such differences between physicians and specialists.

The first author of this paper moved from the renal division to the department of general practice in the same medical school hospital 6 years ago and became aware of big differences between doctors working in these two areas. One notable difference was that physicians showed little interest in mild renal insufficiency and did not know how to use ACEIs appropriately for patients with mild renal failure. The author realized that this might be a serious problem if such differences existed nationwide.

Our results show that such differences are evident and critical in our country. Most physicians do not want to refer to nephrologists for mild renal insufficiency. Moreover, many physicians did not select similar treatment to nephrologists for mild renal insufficiency. This means that many Japanese physicians make different decision from nephrologists for renal insufficiency, which may worsen renal function.

Several criticisms: the adequacy of the sample, the adequacy of the evaluation of renal function, and the universality of the result, can be made of this study.

In Japan, selection of representative physicians for this study is difficult since there are few established training and certification systems for primary-care physicians in Japan. Graduates from one medical school in Japan were selected as representative general physicians for this study. The medical school was established 33 years ago with the aim of improving rural medicine, and all graduates of the medical school have an obligation to work in rural areas for a certain period. Most of them had training and clinical experience as general physicians. All of the physicians selected for this study were certified by the Japanese Society for Internal Medicine. The physicians selected for this study were therefore considered to be representative physicians in Japan.

There might be criticism concerning the use of serum creatinine as a marker of renal function in this study. In the

Table 1 Characteristics of nephrologists and physicians

	Nephrologist ($n = 114$)	Physician ($n = 111$)
Career (years)	18.4 ± 4.8*	15.6 ± 5.8
Gender (male/female)	103/11	106/4
Population	425,000 ± 544,000*	128,000 ± 273,000
Final training in nephrology (%)	As specialist, 88.6	As resident, 76.6
Experience of renal biopsy (%)	99.1*	75.7
Experience of dialysis (%)	98.2*	52.4
Daily renal patients	18 ± 19*	0.71 ± 1.8
Use serum creatinine for outpatient (%)	96.5	95.5
Use creatinine clearance for outpatient (%)	75.4*	34.8

* $P < 0.05$