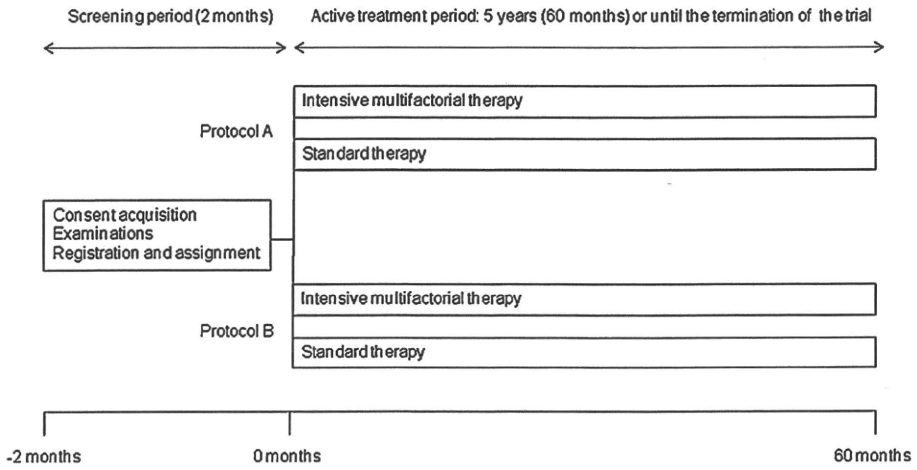

Fig. 1 – Overview of the design of DNETT-Japan.

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.

REFERENCES

[1] Japanese Society for Dialysis Therapy, Condition as of December 31, 2007, in: An Overview of Regular Dialysis Treatment in Japan, Japanese Society for Dialysis Therapy, 2008, pp. 2–22 (in Japanese).
[2] M.J. Sarnak, A.S. Levey, A.C. Schoolwerth, J. Coresh, B. Culleton, L.L. Hamm, et al., Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention, Circulation 108 (2003) 2154–2169.
[3] W.A. Wilmer, B.H. Rovin, C.J. Hebert, S.V. Rao, K. Kumor, L.A. Hebert, Management of glomerular proteinuria: a commentary, J. Am. Soc. Nephrol. 14 (2003) 3217–3232.
[4] P. Gaede, P. Vedel, H.H. Parving, O. Pedersen, Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study, Lancet 353 (1999) 617–622.
[5] P. Gaede, P. Vedel, N. Larsen, G.V. Jensen, H.H. Parving, O. Pedersen, Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes, N. Engl. J. Med. 348 (2003) 383–393.
[6] S. Araki, M. Haneda, T. Sugimoto, M. Isono, K. Isshiki, A. Kashiwagi, et al., Factors associated with frequent remission of microalbuminuria in patients with type 2 diabetes, Diabetes 54 (2005) 2983–2987.
[7] S. Matsuo, E. Imai, M. Horio, Y. Yasuda, K. Tomita, K. Nitta, et al., Revised equations for estimated GFR from serum creatinine in Japan, Am. J. Kidney Dis. 53 (2009) 982–992.
[8] UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment, risk of complications in patients with type 2 diabetes, (UKPDS, 33), Lancet 352 (1998) 837–853.
[9] H.C. Gerstein, M.E. Miller, R.P. Byington, D.C. Goff Jr., J.T. Bigger, J.B. Buse, et al., Effects of intensive glucose lowering in type 2 diabetes, N. Engl. J. Med. 358 (2008) 2545–2559.
[10] Y. Ohkubo, H. Kishikawa, E. Araki, T. Miyata, S. Isami, S. Motoyoshi, et al., Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, Diabetes Res. Clin. Pract. 28 (1995) 103–117.
[11] American Diabetes Association, Diabetic nephropathy: diagnosis, prevention, and treatment, Diabetes Care 25 (2002) 85S–89S.
[12] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo Jr., et al., The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report, JAMA 289 (2003) 2560–2572.
[13] G.F. Strippoli, M. Craig, J.J. Deeks, F.P. Schena, J.C. Craig, Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review, BMJ 329 (2004) 828.
[14] H. Makino, M. Haneda, T. Babazono, T. Moriya, S. Ito, Y. Iwamoto, et al., Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes, Diabetes Care 30 (2007) 1577–1578.
[15] H.H. Parving, H. Lehnert, J. Brochner-Mortensen, R. Gomis, S. Andersen, P. Arner, The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes, N. Engl. J. Med. 345 (2001) 870–878.
[16] B.M. Brenner, M.E. Cooper, D. de Zeeuw, W.F. Keane, W.E. Mitch, H.H. Parving, et al., Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy, N. Engl. J. Med. 345 (2001) 861–869.
[17] E.J. Lewis, L.G. Hunsicker, W.R. Clarke, T. Berl, M.A. Pohl, J.B. Lewis, et al., Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes, N. Engl. J. Med. 345 (2001) 851–860.
[18] C.E. Mogensen, S. Neldam, I. Tikkanen, S. Oren, R. Viskoper, R.W. Watts, et al., Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study, BMJ 321 (2000) 1440–1444.
[19] P. Gaede, H. Lund-Andersen, H.H. Parving, O. Pedersen, Effect of a multifactorial intervention on mortality in type 2 diabetes, N. Engl. J. Med. 358 (2008) 580–591.

Optimal cut-off point of waist circumference for the diagnosis of metabolic syndrome in Japanese subjects

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ABSTRACT

Metabolic syndrome (MetS) has been redefined by a new criterion in Japan, in which waist circumference cut-off points, that is 85 cm for men and 90 cm for women, are used; however, objections are rising against this criterion. The present study examined the criterion for waist circumference to predict the accumulation of the components of MetS. In the present study, we used data for 5972 Japanese people who received annual health examinations, and 621 men (16.3%) and 51 women (2.4%) were diagnosed as having MetS. A cut-off point as a predictor for two or more components of MetS was evaluated by the sensitivity/specificity and a receiver operating characteristic analysis. The optimal point of waist circumference was estimated as being approximately 84 cm for men and 80 cm for women. We therefore recommend revising the cut-off value for the criterion of MetS in women according to our results and studies from other investigators. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00020.x, 2010)

KEY WORDS: Metabolic syndrome, Waist circumference, Cut-off point

INTRODUCTION

Metabolic syndrome (MetS), which is defined by multiple risk factors, including central obesity, high blood pressure, dyslipidemia, and high fasting blood glucose; and persons with MetS have an elevated risk of developing cardiovascular disease (CVD), which is correlated with all-cause mortality[1]. Because the morbidity and mortality of CVD is rapidly increasing worldwide[2], establishing appropriate screening for MetS is essential to prevent the initiation and progression of CVD.

To date, internationally recognized definitions of MetS have been released, namely the criteria of the World Health Organization (WHO)[3], the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III)[4], and the International Diabetes Federation (IDF)[5]. In Japan, a criterion for MetS has been defined as the presence of central obesity (85 cm for men and 90 cm for women) plus any two of the following three factors; (i) dyslipidemia; (ii) high blood pressure; and (iii) impaired fasting glucose[6]. In contrast, the IDF recommended cut-off levels of 90 cm for men and 80 cm for women for central obesity in Asian individuals[5]. There has been controversy as to which of these cut-off points of waist circumference is better for diagnosing central obesity in Japanese men and women. The aim of the present article is to re-evaluate the waist circumference for detecting the risk factor accumulation of MetS in Japanese subjects.

SUBJECTS AND METHODS

The total number of participants in the present study was 5972 (3811 men and 2161 women), aged 20–79 years, who received annual health examinations at Okayama Red Cross General Hospital with informed consent. We measured waist circumference at the umbilical level. MetS was defined among men and women as waist circumferences in excess of 85 cm and 90 cm[6], respectively, in addition to having two or more of the following components: (i) dyslipidemia: triglycerides ≥ 150 mg/dL and/or HDL cholesterol <40 mg/dL; (ii) high blood pressure: blood pressure ≥ 130/85 mmHg; and (iii) impaired fasting glucose: fasting plasma glucose ≥ 110 mg/dL[6]. If an individual was receiving drug therapy for hypertriglyceridemia, low HDL cholesterol, high blood pressure or diabetes mellitus, each item was recorded as a positive finding regardless of the data. To identify the optimal cut-off point of waist circumference as a predictor of the presence of at least two components comprising the MetS, we carried out receiver operating characteristic (ROC) analysis. The statistical software SPSS for Windows (version 8.0; SPSS, Chicago, IL, USA) was used for the analysis.

RESULTS

The mean age of the study subjects was 49.9 ± 10.1 years for men and 48.6 ± 9.4 years for women. Among the 5972 Japanese subjects, 1744 men (45.8%) had a waist circumference in excess of 85 cm and 216 women (10.0%) had a waist circumference

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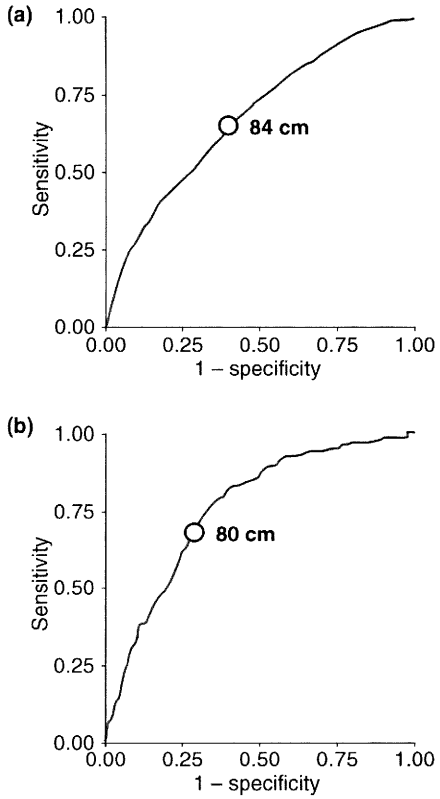

Figure 1 | Receiver operating characteristic (ROC) curve of waist circumference for detecting two or more risk factors of the metabolic syndrome in (a) men and (b) women. O, Cut-off waist circumference yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors.

exceeding 90 cm. In addition, the prevalence of MetS according to the Japanese diagnostic criteria was 621 (16.3%) for men and 51 (2.4%) for women.

We investigated the sensitivity and specificity of waist circumference in predicting the association with two or more metabolic risk factors; that is dyslipidemia, high blood pressure and impaired fasting glucose. In men, the sensitivity and specificity of the waist circumference criterion, that is 85 cm, were 64.2% and 60.2%, respectively. However, in women, the sensitivity and specificity of waist circumference criterion, that is 90 cm, were found to be 29.3% and 91.5%, respectively. A cut-off point as a predictor for two or more components of MetS was evaluated by sensitivity/specificity curves, as well as a ROC curve. The optimal point yielding the maximal sensitivity plus specificity for predicting two or more risk factors was estimated to be approximately 84 cm (sensitivity: 66.3%, specificity: 59.4%) of waist circumference for men and 80 cm (sensitivity: 69.0%, specificity: 65.4%) for women (Figure 1). Based on these findings, 1966 men (51.6%) and 718 women (33.2%) had a waist circumference exceeding 84 cm and 80 cm, respectively. In addition, 675 men (17.7%) and 119 women (5.5%) were diagnosed as having MetS by using 84 cm for men and 80 cm for women as the waist circumference criterion.

DISCUSSION

The IDF has used a waist circumference cut-off value of 90 cm for men and 80 cm for women as its diagnostic criteria of MetS for Asians[5]. In contrast, the waist circumference cut-off value for Japanese was 85 cm for men and 90 cm for women, which correspond to 100 cm^2 of intraperitoneal visceral fat in a cross-section at the height of the navel as shown by computed tomography (CT) both for men and women[6]. To address this controversial point, we re-evaluated the cut-off points of waist circumference for the diagnosis of MetS using ROC analysis. We proposed that the optimal cut-off points are 84 cm for men and 80 cm for women for predicting the clustering of the components of MetS. In men, the criterion of waist circumference deduced from the present study was matched to that of the criterion of MetS in Japan. However, in women, the cut-off value of waist circumference in the present study was lower than that of the criterion.

The first report that estimated the waist circumference cut-off value for diagnosis of MetS in Japan was a study of 3574 employees of a telephone company and their family members (2947 men and 627 women). It estimated the optimal cut-off value for the intraperitoneal visceral fat area at the height of the navel, as determined by CT, to be 100 cm^2 for men and 65 cm^2 for women. Based on these findings, the corresponding cut-off value for waist circumference is 86 cm for men and 77 cm for women[7]. Hara *et al.* also calculated the optimal cut-off point of waist circumference among 692 healthy subjects (408 men and 284 women). and the value of 85 cm for men and 78 cm for women yielded the maximal sensitivity plus specificity for predicting the presence of multiple risk factors[8]. Other studies also reported that the optimal cut-off point for men ranges from approximately 85 to 90 cm; however, in women it ranges from 77 to 83 cm, approximately 80 cm overall (Table 1)[9–15].

Table 1 | Reports on optimal cutoff point of waist circumference for the diagnosis of metabolic syndrome in Japan

Author (reference number)	No. subjects	Cut-off point for men (cm)	Cut-off point for women (cm)
Miyawaki T *et al.*[7]	3574	86	77
Hara K *et al.*[8]	692	85	78
Miyatake N *et al.*[9]	3185	85	80
Nishimura R *et al.*[10]	2113	85	81
Eguchi M *et al.*[11]	420	83	78
Narisawa S *et al.*[12]	12,725	87	83
Oka R *et al.*[13]	1870	89	82
Sato A *et al.*[14]	395	87	80
Doi Y *et al.*[15]	2452	90	80
Present study	5972	84	80

Table 2 | Reports on optimal cut-off point of waist circumference for the diagnosis of metabolic syndrome in Asian countries

Country (reference number)	No. subjects	Cut-off point for men (cm)	Cut-off point for women (cm)
Singapore[16]	4723	90	80
India[17]	640	90	80
Korea[18]	6561	85	80
China[19]	1140	90	85
Korea[20]	31,076	83	76
Korea[21]	4677	84–86	78–80

The cut-off points of waist circumference for MetS suggested by the NCEP-ATP III (102 cm for men and 88 cm for women) are accepted in Western countries and there are no studies that consider whether the optimal cut-off value should be revised. In contrast, several studies that were carried out in Asian countries show that the cut-off values should be lower than those of the NCEP-ATP III (Table 2)[16–21]. Although the cut-off values are defined by the IDF for Asian populations as 90 cm for men and 80 cm for women, several studies from Korea[18,20,21] and China[19] suggest that the optimal cut-off points are different from those of the IDF. Taking these findings together with those of the studies from Japan (Table 1) and Asian countries (Table 2), ethnic differences are likely to exist between populations across Asia, and the criteria for defining MetS in Japan needs to be revised.

The present study has potential limitations. First, the subjects enrolled in our study chose to undergo annual health examinations; they were therefore more health-conscious than average, which might have caused some bias in the current study. Second, the cross-sectional study design makes it difficult to infer causality between waist circumference and metabolic risk factors. Finally, it is still controversial whether or not the waist circumference cut-off values of MetS are significant predictors of cardiovascular events. McNeil *et al.* assessed the association between MetS, using the NCEP III definition, and CVD with an 11-year follow-up period, and they reported that waist circumference is not a significant predictor for CVD[22]. Therefore, our findings are not fully applicable to clinical and public health practice settings. Further studies are needed to prospectively relate the accumulation of visceral fat to the presence of risk factors of CVD.

In conclusion, although follow-up studies are required to prove the feasibility of the definition of MetS to predict the development of CVD, the cut-off value of waist circumference as a criterion for MetS in Japan should be 80 cm for women based on the present results and a review of the literature.

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REFERENCES

1. Lakka HM, Laaksonen DE, Lakka TA, *et al.* The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; 288: 2709–2716.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415–1428.
3. World Health Organization. *Definition, Diagnosis and Classification of Diabetes and its Complications: Report of a WHO Consultation.* WHO, Geneva, 1999.
4. Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). *JAMA* 2001; 285: 2486–2497.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; 23: 469–480.
6. An examination committee for criterion of metabolic syndrome. Definition and criteria of metabolic syndrome. *Nippon Naika Gakkai Zasshi (in Japanese)* 2005; 94: 794–809.
7. Miyawaki T, Hirata M, Moriyama K, *et al.* Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad* 2005; 81 (Ser. B): 471–479.
8. Hara K, Matsushita Y, Horikoshi M, *et al.* A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; 29: 1123–1124.
9. Miyatake N, Wada J, Matsumoto S, Nishikawa H, Makino H, Numata T. Re-evaluation of waist circumference in metabolic syndrome: a comparison between Japanese men and women. *Acta Med Okayama* 2007; 61: 167–169.
10. Nishimura R, Nakagami T, Tominaga M, Yoshiike N, Tajima N. Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan. *Diabetes Res Clin Pract* 2007; 78: 77–84.
11. Eguchi M, Tsuchihashi K, Saitoh S, *et al.* Visceral obesity in Japanese patients with metabolic syndrome: reappraisal of diagnostic criteria by CT scan. *Hypertens Res* 2007; 30: 315–323.
12. Narisawa S, Nakamura K, Kato K, Yamada K, Sasaki J, Yamamoto M. Appropriate waist circumference cutoff values for persons with multiple cardiovascular risk factors in Japan: a large cross-sectional study. *J Epidemiol* 2008; 18: 37–42.
13. Oka R, Kobayashi J, Yagi K, *et al.* Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. *Diabetes Res Clin Pract* 2008; 79: 474–481.
14. Sato A, Asayama K, Ohkubo T, *et al.* Optimal cutoff point of waist circumference and use of home blood pressure as a definition of metabolic syndrome: the Ohasama study. *Am J Hypertens* 2008; 21: 514–520.

15. Doi Y, Ninomiya T, Hata J, *et al.* Proposed criteria for metabolic syndrome in Japanese based on prospective evidence: the Hisayama study. *Stroke* 2009; 40: 1187–1194.
16. Tan CE, Ma S, Wai D, Chew SK, Tai ES. Can we apply the National Cholesterol Education Program Adult Treatment Panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; 27: 1182–1186.
17. Misra A, Wasir JS, Pandey RM. An evaluation of candidate definitions of the metabolic syndrome in adult Asian Indians. *Diabetes Care* 2005; 28: 398–403.
18. Lee SY, Park HS, Kim DJ, *et al.* Appropriate waist circumference cutoff points for central obesity in Korean adults. *Diabetes Res Clin Pract* 2007; 75: 72–80.
19. Bao Y, Lu J, Wang C, *et al.* Optimal waist circumference cutoffs for abdominal obesity in Chinese. *Atherosclerosis* 2008; 201: 378–384.
20. Kim HK, Kim CH, Park JY, Lee KU. Lower waist-circumference cutoff point for the assessment of cardiometabolic risk in Koreans. *Diabetes Res Clin Pract* 2009; 85: 35–39.
21. Baik I. Optimal cutoff points of waist circumference for the criteria of abdominal obesity: comparison with the criteria of the International Diabetes Federation. *Circ J* 2009; 73: 2068–2075.
22. McNeill AM, Rosamond WD, Girman CJ, *et al.* The metabolic syndrome and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. *Diabetes Care* 2005; 28: 385–390.

糖尿病腎症のエビデンス

Evidence of Treatment of Diabetic Nephropathy

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高血圧症を合併する糖尿病腎症患者を対象としたIDNT試験において，ARBであるイルベサルタンの腎保護作用が証明された．糖尿病腎症の治療において，ARBを第一選択薬とする根拠となった先駆的な試験である．

目　的

糖尿病腎症の治療において，血糖および血圧のコントロールが重要であることは，多くのランダム化比較試験(randomized controlled trial；RCT)により証明されている．とくに血圧コントロールに関しては，**レニン・アンジオテンシン系阻害薬**を第一選択薬とする厳格な血圧コントロールが必要とされている．また，腎症発症阻止を検討した試験や，**早期腎症**あるいは**顕性腎症**を対象とした試験など，異なる病期を対象にした試験が報告されている．本稿では，持続性蛋白尿が出現する顕性腎症の2型糖尿病患者に対するアンジオテンシンⅡ受容体拮抗薬(angiotensinⅡreceptor blocker；ARB)の腎保護作用を証明したIDNT(Irbesartan Diabetic Nephropathy Trial)試験[1]について解説する．

対象と方法

多施設共同，二重盲験並行群間比較試験で，30～70歳の血清クレアチニン上昇(男性1.2～3.0mg/dL，女性1.0～3.0mg/dL)を伴う2型糖尿病，持続性蛋白尿(蛋白尿900mg/日以上)を合併する高血圧患者1,715例を対象とした．イルベサルタン(75～300mg/日)群，アムロジピン(2.5～10mg/日)群，またはプラセボ群にランダムに割り付けた．目標血圧は，すべての群で135/85mmHg以下であった．一次エンドポイントは血清クレアチニンの倍増，末期腎不全または全死亡発症までの期間と定義した．二次エンドポイントとしては心血管死，非致死的心筋梗塞，入院が必要な心不全，脳血管障害に起因する永続的な神経障害，下肢切断とした．

結　果(図)

追跡調査の平均期間は2.6年間であった．イルベサルタンの治療は，主要複合エンドポイントのリスクがプラセボ群のリスクよりも20％低く(p＝0.02)，アムロジピン群のリスクよりも23％低い(p＝0.006)ことに関連していた．血清クレアチニン濃度が2倍になるリスクは，イルベサルタン群がプラセボ群よりも33％低く(p＝0.003)，アムロジピン群よりも37％低かった(p＜0.001)．イルベサルタンの治療は，末期腎不全の相対危険度が，ほかの2群よりも23％低下したことに関連していた(どちらの群との比較でも，p＝0.07)．これらの差は，到達血圧の差によっては説明されなかった．血清クレアチニン濃度の上昇は，イルベサルタン群では，プラセボ群よりも24％遅く(p＝0.008)，アムロジピン群よりも21％遅かった(p＝0.02)．全死亡率あるいは心血管の複合エンドポイントには，有意差は認められなかった．

結　論

ARBのイルベサルタンは，2型糖尿病患者での腎症の進行を保護するのに有効である．この保護作

用語解説――レニン・アンジオテンシン系阻害薬
ACE阻害薬およびARBは，アンジオテンシンの作用を阻害する降圧薬で，糖尿病を合併する高血圧治療において第一選択薬となっている．

用語解説――早期腎症・顕性腎症
糖尿病腎症の病期において，微量アルブミンが検出される時期を早期腎症，持続的に蛋白尿が認められる時期を顕性腎症という．

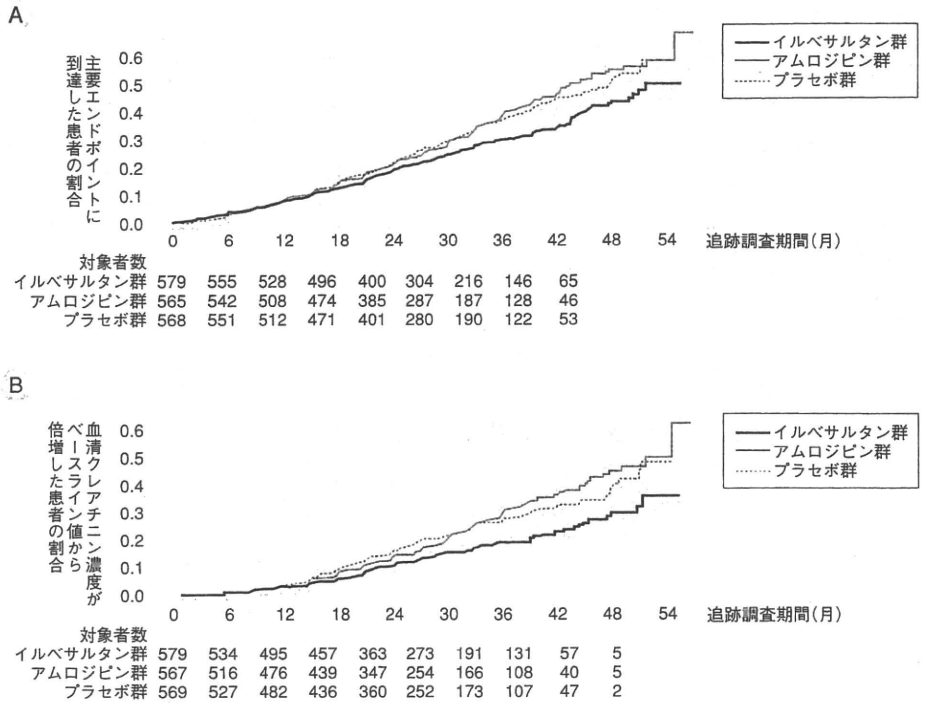

図　IDNTにおける主要エンドポイント(A)とその構成項目である血清クレアチニン濃度のベースライン値から倍増(B)に達した患者の累積割合

用は，この薬剤がもたらす血圧降下とは独立している．

臨床への適応

糖尿病患者に高血圧症や蛋白尿を合併することは，日常診療においてしばしば経験する．IDNT試験は，高血圧症を合併する顕性腎症の2型糖尿病患者を対象に，ARBであるイルベサルタンの腎保護作用を証明した先駆的な試験であるといえる．また顕性腎症に対するARBの腎症進展抑制効果を検討した試験としては，ロサルタンを用いたRENAAL試験[2]がある．

臨床上，持続性蛋白尿が出現するようになると血圧コントロールが難しく，また心血管イベントを多く発症し治療に難渋することが多い．したがって，より早い段階から積極的に血糖・血圧コントロールを行うことが重要である．早期腎症に対するARBの効果を検討したRCTとしては，IRMA 2[3] (Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria)，MARVAL[4] (Microalbuminuria with Valsartan)，INNOVATION[5] (Incipient to Overt：Angiotensin Ⅱ Receptor Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy)試験などが挙げられる．糖尿病腎症を対象としたRCTは海外で行われたものが多いが，INNOVATION試験はわが国において実施された試験であり，その点で特筆すべきといえる．

References

1) Lewis EJ et al：N Engl J Med 345：851-860, 2001
2) Brenner BM et al：N Engl J Med 345：861-869, 2001
3) Parving HH et al：N Engl J Med 345：870-878, 2001
4) Viberti G et al：Circulation 106：672-678, 2002
5) Makino H et al：Diabetes Care 30：1577-1578, 2007

関連事項

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ORIGINAL ARTICLE

Design and methods of a strategic outcome study for chronic kidney disease: Frontier of Renal Outcome Modifications in Japan

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Abstract
Background The continuous increase in the number of people requiring dialysis is a major clinical and socioeconomical issue in Japan and other countries. This study was designed to encourage chronic kidney disease (CKD) patients to consult a physician, enhance cooperation between nephrologists and general practices, and prevent the progression of kidney disease.

Methods Subjects comprise CKD patients aged between 40 and 74 years consulting a general physician, and patients in CKD stage 3 with proteinuria and diabetes or hypertension. This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four

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regions (strata) based on the level of increase rate of dialysis patients. The patients in group A clusters were instructed initially to undergo treatment in accordance with the current CKD treatment guide, whereas patients in group B clusters were not only instructed in the same fashion but also received support from an information technology (IT)-based system designed to help achieve the goals of CKD treatment, consultation support centers, and consultations by dietitians visiting the local general practice offices. We assessed the rates of continued consultation, collaboration between general practitioners and nephrologists, and progression of CKD (as expressed by CKD stage).

Conclusion Through this study, filling the evidence-practice gap by facilitating effective communication and supporting general physicians and nephrologists, we will establish a CKD care system and decrease the number of advanced-stage CKD patients.

Keywords Chronic kidney disease · Evidence-practice gap · Cluster-randomized study · Educational intervention · Cooperation between nephrologists and general physicians

Introduction

The number of dialysis patients is continually increasing, with consequent rises in medical costs for the treatment of end-stage kidney disease (ESKD) patients becoming a socioeconomical concern worldwide. In fact, there are 2,153.2 dialysis patients per million of population in Japan [1]. Chronic dialysis treatment not only reduces the quality of life (QOL) of patients [2, 3] but also places considerable financial strain on society, with annual medical costs of five to six million yen per dialysis patient, or total expenses of one trillion yen. Moreover, it is estimated that there are more than ten million chronic kidney disease (CKD) patients in Japan [4]. Previous studies suggested that CKD is one of the most important risk factors for cardiovascular disease, among known risk factors of diabetes, hypertension, hyperlipidemia, obesity, smoking, and lifestyle-related disease [5–8]. Therefore, early detection and control of CKD are also important in terms of preventing cardiovascular complications and deaths.

The definition of CKD first appeared in the Kidney Disease Outcome Quality Initiative (KDOQI) Guidelines issued by the National Kidney Foundation (NKF) in 2002 [9], and was revised by Kidney Disease: Improving Global Outcomes (KDIGO) in 2005 [10]. Since then, the definition of CKD and renal function assessment methods are being accepted worldwide. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. The concept of CKD comprehensively addresses a wide range of kidney patients, including ESKD and transplant patients. It is important to establish appropriate, consistent, and specific treatment and prevention-based care systems according to the progression of kidney disease. The Ministry of Health, Labor, and Welfare organized a study group to design strategic outcome studies and discuss the following research subjects: prevention of diabetes, prevention of suicide and depression (2005), cancer prevention, and AIDS/HIV prevention (2006), which have been started. Following these studies, a strategic study to improve the progression of CKD was planned based on these social and scientific demands to reduce new patients with initiation of renal replacement therapy due to ESKD, termed the Frontier of Renal Outcome Modifications in Japan (FROM-J).

Diabetic nephropathy, nephrosclerosis due to hypertension, and chronic glomerulonephritis are three major primary renal diseases in ESKD, not only in Japan but also in Western countries [1]. In Japan, the proportion of new ESKD patients due to chronic glomerulonephritis has recently been decreasing, while that of diabetic nephropathy is rapidly increasing. If this trend continues, in 5 years, patients undergoing dialysis due to diabetic nephropathy will account for 50.82% of the total whereas those with chronic glomerulonephritis will account for 19.54%. In other words, the primary renal disease in half of dialysis patients will be diabetic nephropathy, and the number of dialysis patients with chronic glomerulonephritis will decrease by 17%. The decreasing trend in chronic glomerulonephritis is due to annual urinalysis screening programs established by the Japanese government [11]. Also, more attention should be paid to preventing deterioration of renal function in patients with diabetic nephropathy and nephrosclerosis.

Although diabetic nephropathy is the primary underlying disease in dialysis patients in many developed countries, it has been showing a decreasing trend in some regions and countries, including Denmark. In Denmark, after a steady increase from 52 in 1990 to 183 in 2002, the number of dialysis patients with diabetic nephropathy decreased by 15%, to 155–156 patients per million people [12]. This indicates that aggressive management of both blood pressure and glucose, administration of renin angiotensin system (RAS) inhibitors, and advice on lifestyle can reduce ESKD with diabetic nephropathy by more than 15%. According to the 2002 diabetes survey conducted by the Ministry of Health, Labor, and Welfare of Japan, only 33.3% of patients in Japan had controlled their HbA1c to less than 6.5%, and these interventions are expected to achieve marked effects. Furthermore, although 50.2% of males and 38.3% of females aged 40 years or

older in Ibaraki Prefecture showed hypertension, only 41.9% and 49.2% of them, respectively, were receiving antihypertensive treatment [13], and blood pressure was not adequately controlled in about 50% of those who were receiving treatment [14]. Appropriate interventions are assumed to bring about noticeable effects in Japan, in which RAS inhibitors have not been used effectively as antihypertensive therapy, although a slight increase has occurred in recent years [15].

Recently, the CKD Clinical Practice Guide for future treatment methods was developed by the Japanese Society of Nephrology [16], describing the treatment target for every CKD stage. Although all items of the treatment method were supported by clinical evidence, there were no prospective studies showing the effect of practices such as the CKD Clinical Practice Guide targets on renal and cardiovascular outcomes in sufficient number of CKD patients.

In this strategic CKD study, a prospective stratified cluster-randomized trial to examine the effectiveness of a care system designed to prevent progression of CKD through collaboration between nephrologists and general physicians was selected. One of the goals of the study is a 15% reduction in the estimated number of new dialysis patients in 5 years by increasing the rates of compliance with the CKD Clinical Practice Guide. The study also aims to encourage CKD patients to see their family physician, consult a nephrologist, and receive nutritional and lifestyle advice, while discussing health care measures to reduce the number of new dialysis patients.

Hypotheses of study

The study hypothesis encompasses the following four core issues:

1. Clinical practice in accordance with the Japanese CKD Clinical Practice Guide will improve the prognosis of CKD patients and reduce the speed of renal function deterioration.
2. Education-based interventions for CKD patients by registered dietitians and other co-medicals will help achieve strict CKD treatment goals in accordance with the Japanese CKD Clinical Practice Guide.
3. Collaboration concerning clinical practices among general physicians, nephrologists, and co-medicals will reduce the gap between clinical practice and evidence-based care measures, and improve the rate of continued consultation and prognosis in CKD patients.
4. These active interventions to improve CKD treatment will achieve the desired effects in terms of medico-economics.

Subjects and methods

Study organization and duration

Since the increase in the rate of dialysis patients varies from region to region in Japan [17], we divided the country into four regions (Fig. 1) as strata, so that they would

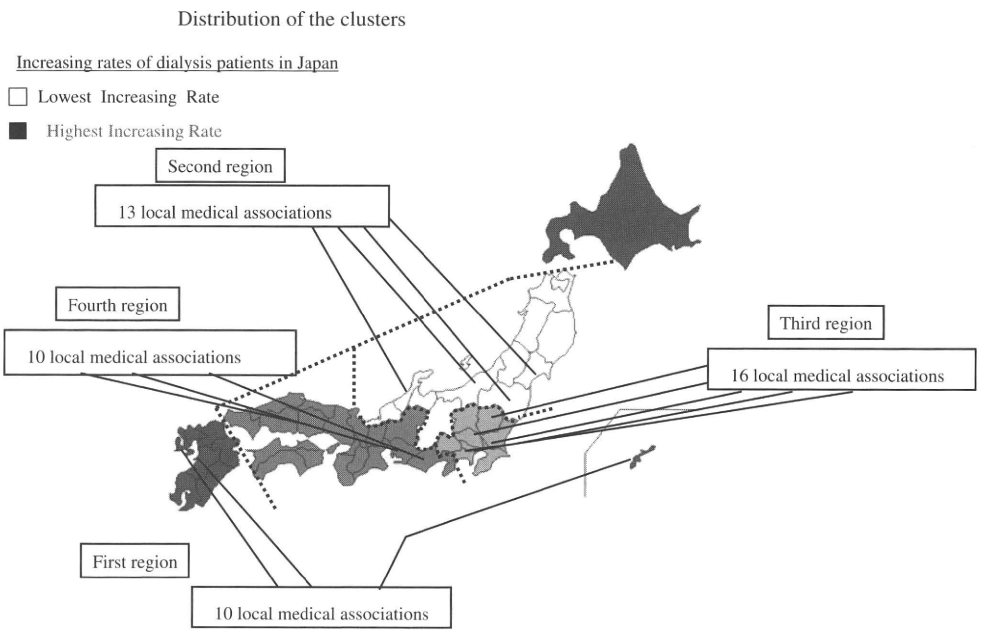

Fig. 1 Distribution of the clusters. We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients [17]

include at least one managing facility and two or more clusters. The primary intervention study duration is from October 2008 to March 2012.

Rationale for setting the number of patients

This project aims to examine whether or not intervention can reduce the incidence of dialysis patients by 15% over the next 5 years. Regarding the calculation, we estimated the annual decrease in GFR as 0.59 ml/min/year (standard deviation (SD) 0.04 ml/min/year), based on changes in renal function among healthy Japanese people who underwent health checkups [17, 18] and the rate of renal deterioration in patients in CKD stage 3 with diabetes or hypertension [mean serum creatinine = 1.69 mg/dl (SD = 0.57 mg/dl), annual decrease rate = 5.93 ml/min/year (SD 4.321 ml/min/year), $n = 569$] [18, 19]. The required study size was calculated as 2,038 when the unknown intracluster correlation coefficient was assumed to be 0.5. We determined the required number as 2,264 for groups A and B, assuming that 10% would withdraw. We applied the simple number of 2,500 (1,250 for each group) as the target number of patients to perform this study.

Eligible patients

Each registered general physician obtained written informed consent for the study from eligible patients. They were formerly registered after the data center verified their eligibility. Inclusion criterion were: (1) age between 40 and 74 years; (2) in CKD stage 1, 2, 4, or 5; (3) in CKD stage 3 with proteinuria (ratio of urinary protein/urinary creatinine $\geq$0.3, or proteinuria $\geq$1+) and diabetes or hypertension.

Dialysis patients and those who did not consent were excluded from this study.

Assignment and randomization

This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients (Fig. 1). Each local medical association recruited 10–58 general physicians by whom patients in this study has been treated. Local medical associations are randomized when the enrolment period is completed.

Intervention methods

Patients in group A clusters are instructed initially to undergo treatment in accordance with the current CKD treatment guide only, whereas patients in group B clusters are not only instructed in the same fashion but also receive consultations by dietitians visiting the local general practice offices. In addition, the data center closely monitors the treatment status and provides the group B general practice office with comments on the data.

Goals for the treatment of chronic kidney disease (groups A and B)

Participants in the study, or patients, will receive treatment according to the CKD Clinical Practice Guide [16]. Table 1 shows a summary of targets for CKD treatment applied to all patients. In patients with CKD, lifestyle modifications to avoid obesity and stop smoking are necessary. Strict blood pressure control (less than 130/80 mmHg), strict blood sugar control (HbA1c <6.5%), and low-density lipoprotein (LDL)-cholesterol control (LDL-C <120 mg/dl) are shown as targets for CKD treatment. The standards for referral from general physicians to nephrologists are as follows: (1) ratio of urinary protein/urinary creatinine $\geq$0.5, or proteinuria $\geq$1+; (2) estimated GFR (eGFR) <50 ml/min/1.73 m^2; (3) both proteinuria and hematuria positive ($\geq$1+); and (4) when family physicians judge that patients should consult a nephrologist. Estimated GFRs in this study are calculated using the following formula:

$$\mathrm{eGFR(ml/min/1.73\ m^2)} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cre}^{-1.094} (\times 0.739 \text{ in the case of women}).$$

Monitoring of treatment status by the data center (only group B)

The data center closely monitors the treatment status and provides the group B general practice office with comments on the data. In addition, the data center will provide information on the patients scheduled to visit the office, examinations, and treatment that patients should undergo on their next visit, patients who did not visit hospitals as scheduled, those who are going to receive lifestyle/dietary advice, and those who meet the conditions for referral to nephrologists. The center also monitors patients and their schedules: the next consultation date, required examinations, details of treatment and care provided, and advice on lifestyle and nutrition. The centers will contact patients by mail, telephone, or email a week before the consultation day and encourage those who have not consulted a physician for over 2 months to receive care, trying to prevent their withdrawal from treatment. To facilitate referrals to nephrologists, the centers send a list of patients who meet the criteria for referral to the physicians and clinical research coordinators (CRCs).

Table 1 CKD practice guide target in this study

CKD stages	Lifestyle	Diet	Blood pressure	Blood sugar	Lipid metabolism	Hemoglobin
Stage 1	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 2	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 3	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6-0.8 g/kg/day	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 4	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 5	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Others			<125/75 mmHg If proteinuria >1 g/day			

BMI body mass index. *DPI* dietary protein intake

Nutrition and lifestyle improvement (only group B)

Registered dietitians provide support according to the instructions and advice from family physicians. They help patients achieve their CKD treatment goals, explaining to patients about examination results, achievements in CKD care, and their implications. Registered dietitians receive training so that they will be able to provide integrated and consistent advice.

Data collection

At each consultation, physicians will measure patients' blood pressure, and check their blood pressure conditions at home. Examinations or surveys will be performed every 6 months regarding body weight, abdominal circumference, smoking status, fasting serum creatinine, blood urea nitrogen (BUN), potassium, hemoglobin (Hb), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), uric acid, total protein, albumin, fasting blood glucose, HbA1c (only in the case of diabetes), urinary creatinine levels, amount of urinary proteins, eGFR, number of patients referred by nephrologists, number of new dialysis patients, and incidence of cardiovascular events.

Parameters for assessment

Primary parameters for assessment are: (1) the rate of continuous clinic visits of CKD patients, (2) the proportion of patients under cotreatment between general physicians and nephrologists, and (3) annual changes in CKD stage.

Secondary parameters are: (1) the proportion of adherence to the complete CKD treatment guide, (2) the rate of achievement of blood pressure goals, (3) the number of subjects with 50% reduction in urinary protein, (4) the number of subjects with a doubling of serum creatinine or 50% reduction in eGFR, (5) yearly changes in the number of patients starting renal replacement therapy, and (6) the incidence of cardiovascular events.

Statistical analysis

Statistical analyses will be performed using an intent-to-treat approach. Differences in primary endpoints between intervention groups are described by their 95% confidence intervals. The declining velocity of eGFR is tested by analysis of variance, using the efficacy of interventions as fixed effects and cluster effects as random effects. We employ a generalized linear model with age, gender, complications, and previous GFR as covariates where appropriate. The significance level on both sides in hypothesis testing is set at 0.05.

For secondary endpoints, we will use analysis of variance with a generalized linear model.

Ethical considerations

This study is being conducted in accordance with the Ethical Guidelines for Clinical Studies (revised on December 28, 2004, of the Ministry of Health, Labor, and Welfare) and the Ethical Guidelines for Epidemiological Studies (revised on August 16, 2007, of the Ministries of Education, Culture, Sports, Science, and Technology/ Health, Labor, and Welfare). All medical professionals involved in this study must comply with these ethical standards. This study is a Central Institutional Review Board (Central IRB) program, and the Committee on Ethics in Strategic Research of the Kidney Foundation, Japan, will examine and approve implementation plans and their revision.

Discussion

The purpose of this study is to enhance cooperation between nephrologists and general physicians, improve lifestyle and dietary advice provided by registered dietitians at general physicians' offices, and offer measures to control blood pressure and other critical parameters in practice, thereby filling the evidence-practice gap, which will slow the progression of kidney disease.

Recently, the concept of chronic kidney disease has been announced not only in Japan, but also throughout the world [9, 10]. There are more than ten million CKD patients in Japan [4], and so CKD is regarded as a public health problem.

CKD guidelines for general physicians or patients have been published in European countries [9, 20–22]. The USA is also preparing similar measures for CKD [23, 24]. In Japan, annual urinalysis for early detection of renal disease started in the 1970s [11, 25], and a serum creatinine test was included in health examinations as early as 1989 to detect kidney failure among adults aged 40 years or older [26]. However, the number of dialysis patients is increasing by approximately 4% each year. It is necessary to implement more appropriate measures to reduce the rate of new dialysis patients in Japan as soon as possible.

In 2007, the Japanese Society of Nephrology established the CKD Clinical Practice Guide to help family physicians provide care for CKD patients. The guide suggests that lifestyle and dietary advice on obesity prevention [27], smoking cessation [28], and a sodium-restricted diet, and treatment for metabolic disorders [29, 30], hypertension [31], and hyperlipidemia [32] are effective to prevent progression of CKD. However, most people are not making sufficient efforts to manage their own health condition [13]. It is necessary to show the effect on the progression of CKD of treatment as part of the Clinical Practice Guide. Our challenge is to obtain sufficient evidence regarding the efficacy of filling the evidence-practice gap in preventing deterioration of renal function among Japanese patients.

We set the following conditions for patient eligibility in this study: CKD patients aged between 40 and 74 years; patients in CKD stage 1, 2, 4 or 5; and patients in CKD stage 3 with a high level of urinary protein and diabetes or hypertension. Proteinuria is known as the strongest predictor of decreasing renal function [13, 33], and the aggressive management of blood pressure and glucose [29, 31] and administration of RAS inhibitors [34–36] prevent the deterioration of renal function. The reason for the condition regarding urinary proteins in stage 3 patients is that we need to register patients showing significant deterioration in renal function [37].

Regarding lifestyle and dietary advice, we have prepared a list of instructions and advice for individual patients on a priority basis, so that registered dietitians can design a guidance schedule based on the priority list and provide consistent advice. In this study, we focus on preventing progression of CKD in the early stage by giving priority to Japanese CKD practice guide goals. We are preparing a long-term guidance method covering a wide range of health management items while seeking ways to reduce the evidence-practice gap as much as possible.

We predict significant positive effects in intervention group B (increased collaboration in clinical practice) in terms of increases in the rate of continued consultation and collaboration between nephrologists and other physicians, and reduced CKD stage progression as a result of instructions and advice from registered dietitians, compared with intervention group A. This study was designed to examine the effectiveness of a support system for collaborative CKD diagnosis and treatment by conducting a cluster-randomized controlled trial. We expect that this study will help improve clinical practices for CKD patients and provide high-quality clinical findings of global standard. Although the number of CKD patients in Japan is estimated to be more than ten million, there are only 3,000 nephrologists. If effective collaboration is established among nephrologists in CKD care, it will have a significant positive impact on renal care systems. In the area of renal care, few large-scale intervention studies have been performed on kidney care systems, except those aimed to assess the efficacy of drug interventions. Little progress has been made in the development of infrastructure for clinical studies and research environments in Japan. This study is expected not only to help develop the infrastructure required for clinical renal studies but also to generate valuable findings.

Progress of the study

Prior to the study, we selected 15 management facilities and 49 local medical associations, registered 491 family physicians (between April and June 2008), and registered 2,494 study participants on a provisional basis (between April and October 15, 2008), 2,413 of whom were randomly divided into intervention groups A (1,211) and B (1,202) in units of medical associations (or clusters) in September 2008. We started the intervention study on October 20, 2008.

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References

1. Nakai S, Masakane I, Akiba T, Iseki K, Watanabe Y, Itami N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2005). Ther Apher Dial. 2007;11:411–41.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
4. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease (CKD) in Japanese general population. Clin Exp Nephrol, 2009.
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
8. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch Intern Med. 2005;165:2659–65.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–266.
10. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
11. Yamagata K, Takahashi H, Suzuki S, Mase K, Hagiwara M, Shimizu Y, et al. Age distribution and yearly changes in the incidence of end-stage renal disease in Japan. Am J Kidney Dis. 2004;43:433–43.
12. Sorensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark. Kidney Int. 2006;70:187–91.
13. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71:159–66.
14. Heagerty A. Optimizing hypertension management in clinical practice. J Hum Hypertens. 2006;20:841–9.
15. Usami T, Nakao N, Fukuda M, Takeuchi O, Kamiya Y, Yoshida A, et al. Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan. Kidney Int. 2003;64:1445–9.
16. CKD Clinical Practice Guidelines: Japanese Society of Nephrology (written and edited), First edition, Tokyo Igakusha, 2007.
17. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G. Regional variations in the incidence of end-stage renal failure in Japan. JAMA. 2000;284:2622–4.
18. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
20. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13):S289–91.
21. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med. 2005;5:635–42.
22. Nicholls K. Prevention of progression of kidney disease: diabetic nephropathy—CARI guidelines. Aust Fam Physician. 2007;36:137–8.
23. IV. NKF-K/DOQI Clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis. 2001;37:S182–238.
24. Neumann ME. Results in KEEP's first report show progress in early identification of CKD patients. Nephrol News Issues. 2003;17:84–7.
25. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. Nephron. 2002;91:34–42.
26. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
27. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis. 2006;48:383–91.
28. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence?. Clin J Am Soc Nephrol. 2008;3:226–36.
29. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993; 329:977–86.

30. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103–17.
31. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36:646–61.
32. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14:2084–91.
33. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
34. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939–45.
35. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis. 1999;34:809–17.
36. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
37. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90.

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Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease

A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial

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Objectives The purpose of this study was to determine the benefit and risk associated with antiplatelet therapy in the chronic kidney disease (CKD) population.

Background Cardiovascular and possibly bleeding risks are elevated in patients with CKD. The balance of benefit and harm associated with antiplatelet therapy remains uncertain.

Methods The HOT (Hypertension Optimal Treatment) study randomly assigned participants with diastolic hypertension to aspirin (75 mg) or placebo. Study treatment effects were calculated using univariate proportional hazards regression models stratified by baseline estimated glomerular filtration rate (eGFR) with trends tested by adding interaction terms. End points included major cardiovascular events, total mortality, and major bleeding.

Results The study included 18,597 participants treated for 3.8 years. Baseline eGFR was <60 ml/min/1.73 m^2 in 3,619 participants. Major cardiovascular events were reduced by 9% (95% confidence interval [CI]: −9% to 24%), 15% (95% CI: −17% to 39%), and 66% (95% CI: 33% to 83%) for patients with baseline eGFR of ≥60, 45 to 59, and <45 ml/min/1.73 m^2, respectively (p trend = 0.03). Total mortality was reduced by 0% (95% CI: −20% to 17%), 11% (95% CI: −31% to 40%), and 49% (95% CI: 6% to 73%), respectively (p trend = 0.04). Major bleeding events were nonsignificantly greater with lower eGFR (hazard ratio [HR]: 1.52 [95% CI: 1.11 to 2.08], HR: 1.70 [95% CI: 0.74 to 3.88], and HR: 2.81 [95% CI: 0.92 to 8.84], respectively; p trend = 0.30). Among every 1,000 persons with eGFR <45 ml/min/1.73 m^2 treated for 3.8 years, 76 major cardiovascular events and 54 all-cause deaths will be prevented while 27 excess major bleeds will occur.

Conclusions Aspirin therapy produces greater absolute reduction in major cardiovascular events and mortality in hypertensive patients with CKD than with normal kidney function. An increased risk of major bleeding appears to be outweighed by the substantial benefits. (J Am Coll Cardiol 2010;56:956–65) © 2010 by the American College of Cardiology Foundation

Chronic kidney disease (CKD) is common in the general community. Population-based studies have shown that 10% to 15% of the adult population has CKD (1–3), and this proportion is increasing (4). Most people with CKD have relatively mild disease and are unlikely to ever require dialysis or a kidney transplant; however, even early CKD confers an increased risk of cardiovascular events and death (5–11). Recent work has demonstrated that lipid lowering (12) and blood pressure lowering (13,14) are both effective

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in reducing the risk of cardiovascular events in people with early CKD; however, less is known about the balance of risks

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and benefits associated with other potential preventative therapies.

In trials of secondary prevention of cardiovascular disease, treatment with aspirin clearly delivers a net benefit of harm reduction over harm caused. The Antithrombotic Trialists' Collaborative Group meta-analysis of individual participant data confirmed that aspirin reduces the yearly risk of major cardiovascular outcomes (strokes and coronary events) by about 15 events per 1,000 patient-years (15). However, the same analysis demonstrated that, overall, among participants with no history of previous cardiovascular events (primary prevention), the absolute benefit of aspirin in preventing 0.6 events per 1,000 patient-years is comparable to the number of major gastrointestinal and extracranial bleeds caused (0.3 events per 1,000 patient-years). Analyses of the effect of aspirin in a number of defined subgroups failed to identify a primary prevention patient group that benefited from aspirin.

Patients with CKD have high cardiovascular risk; therefore, the absolute benefits of aspirin might be greater for them than for people with normal kidney function. However, patients with CKD have abnormal platelet function, leaving them at potentially increased hemorrhagic risk when treated with anticoagulants, including antiplatelet agents (16). Substantial uncertainty persists regarding the balance between the risks and benefits associated with antiplatelet agents for patients with CKD. Consistent with this uncertainty, patients with CKD (17) and end-stage kidney disease (18) have been shown to be less likely to be prescribed aspirin after an acute myocardial infarction.

The HOT (Hypertension Optimal Treatment) trial, one of the largest individual primary prevention trials, randomly allocated 18,790 participants 50 to 80 years of age with elevated diastolic blood pressure to aspirin or matching placebo for an average of 3.8 years (19). It was a primary prevention study with <2% of participants having a prior history of myocardial infarction. In the HOT study overall, a significant 15% reduction in major cardiovascular events (1.6 events per 1,000 patient-years) was observed, but this needs to be weighed against a significant 80% increase in the risk of major nonfatal bleeding (1.4 events per 1,000 patient-years). Analyses demonstrated there was no interaction between the blood pressure–lowering effect and aspirin effects (19,20). Subsequent analyses of the HOT study population used serum creatinine thresholds to explore how impairment of renal function influences the effect of aspirin (5,6). A trend to increased benefit from aspirin was demonstrated for patients with an elevated serum creatinine. However, the balance of benefits and harms associated with aspirin usage in CKD have not been previously reported, nor has the level of renal function below which benefits may overcome harms been established.

Since these subgroup analyses, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation (21) has become standard in the staging of CKD (22). This analysis, therefore, investigates whether the balance of benefits and harms of aspirin therapy in HOT study participants is influenced by kidney function evaluated continuously and categorically by CKD stage based on eGFR levels.

Abbreviations and Acronyms

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HR = hazard ratio

KDOQI = Kidney Disease Outcomes Quality Initiative

Methods

Participants and HOT trial design. The HOT study design has been described in detail elsewhere (19,23). In brief, 18,790 participants age 50 to 80 years (mean 61.3 years) from 26 countries in Europe, North and South America, and Asia, and with a diastolic blood pressure between 100 and 115 mm Hg, were randomly assigned to 2 interventions in a factorial design: aspirin 75 mg daily (n = 9,399) or matching placebo (n = 9,391), and 1 of 3 diastolic blood pressure targets (≤90, ≤85, or ≤80 mm Hg). The blood pressure targets were randomly assigned in an open-label fashion. There was no exclusion on the basis of renal function. The conduct of the study was overseen by a steering committee and approved by national and local ethics committees and regulatory bodies at all participating centers. An independent safety committee regularly reviewed safety data. All patients provided written informed consent.

The current analysis included 18,597 participants assigned to aspirin or placebo for whom baseline serum creatinine values were available. Analyses of the change in renal function were performed on participants for whom serum creatinine values were also available at study end. Glomerular filtration rate was estimated using the 4-variable Modification of Diet in Renal Disease equation (21) and categorized using Kidney Disease Outcomes Quality Initiative (KDOQI) stages (24).

End points. The primary end point of this study was a composite of major cardiovascular events consisting of myocardial infarction, stroke, and death due to cardiovascular disease. Secondary end points included myocardial infarction (nonfatal myocardial infarction and death due to coronary heart disease [including sudden death]), stroke (fatal and nonfatal stroke), cardiovascular mortality, total mortality, death due to kidney failure, and change in eGFR. Cardiovascular and mortality events were reviewed and validated by an independent clinical event committee. Secondary end points also included investigator-reported major hemorrhage (fatal, life-threatening, disabling, or requiring hospital admission) and minor hemorrhage (all other reported bleeding events). The first event of each relevant outcome type was included for analysis.

Participants were recruited from October 1992 until April 1994, with follow-up concluding in August 1997, resulting in an average follow-up period of 3.8 years (range 3.3 to 4.9 years) (19).

Statistical methods. The risk estimates for each outcome associated with eGFR at baseline were estimated using a

Cox proportional hazards regression model after adjusting for potentially confounding baseline covariates including age, sex, systolic blood pressure, history of diabetes mellitus, history of cardiovascular disease, total cholesterol, body mass index, and smoking. The variances of each risk estimate were calculated using the floating absolute risk method (25,26). The regression lines for the risk estimates according to eGFR at baseline were fitted using linear regression analysis with inverse variance weighting (27).

The effect of randomization to aspirin was assessed according to baseline eGFR categories of ≥60, 45 to 59 (KDOQI CKD stage 3a), and <45 ml/min/1.73 m^2 (KDOQI stage 3b, 4, and 5). The hazard ratio (HR) and 95% confidence interval (CI) associated with active treatment for each end point was estimated using a univariate Cox proportional hazards regression model stratified by eGFR levels at baseline. The presence of heterogeneity in the treatment effect across eGFR categories was assessed by adding an interaction term to the relevant Cox model.

To assess whether there was any threshold level of eGFR, below which the effect of treatment changed, the risk estimate was investigated by fitting univariate Cox proportional hazards model below an eGFR threshold, which was progressively changed using 3 ml/min/1.73 m^2 increments.

The absolute effect of randomization to aspirin was calculated as the number of people in whom events were prevented or caused per 1,000 patients treated for 3.8 years for the overall study population and for categories of kidney function.

Results

The study population, consisting of 18,597 of 18,790 (99.0%) randomized patients with serum creatinine data available, had a median eGFR of 73 ml/min/1.73 m^2 (interquartile range 63 to 84 ml/min/1.73 m^2). Of these, 14,978 (80.5%) had an eGFR ≥60 ml/min/1.73 m^2, 3,083 (16.6%) had an eGFR of 45 to 59 ml/min/1.73 m^2, and 536 (2.9%) an eGFR of <45 ml/min/1.73 m^2 (Table 1). Only 9 patients (0.05%) had an eGFR of <15 ml/min/1.73 m^2.

A total of 671 people experienced at least 1 major cardiovascular event. Strokes were experienced by 289 participants, and myocardial infarctions were experienced by 349. There were 582 deaths from any cause, including 268 deaths from cardiovascular causes and 8 from renal failure (3 in the aspirin group and 5 in the placebo group). There were 15 fatal bleeding events (7 in the aspirin group and 8

Table 1 Baseline Characteristics of Participants According to eGFR Categories and Aspirin Randomization

	eGFR (ml/min/1.73 m^2)					
	≥60		45–59		<45	
Overall	Aspirin (n = 7,517)	Placebo (n = 7,461)	Aspirin (n = 1,527)	Placebo (n = 1,556)	Aspirin (n = 264)	Placebo (n = 272)
eGFR, ml/min/1.73 m^2	77 (69–88)	77 (69–89)	55 (52–58)	55 (52–58)	40 (34–43)	39 (32–43)
Serum creatinine, μmol/l	81 (71–93)	81 (71–93)	99 (92–115)	100 (93–115)	142 (121–174)	150 (121–177)
Characteristics at baseline						
Age, yrs	60.6 ± 7.2	60.6 ± 7.2	65.0 ± 7.5	64.9 ± 7.5	66.1 ± 8.2	66.1 ± 7.9
Female	3,185 (42)	3,197 (43)	1,036 (68)	1,026 (66)	169 (64)	175 (64)
Systolic BP, mm Hg	169 ± 14	169 ± 14	171 ± 15	171 ± 14	173 ± 16	173 ± 16
Diastolic BP, mm Hg	105 ± 3	105 ± 3	105 ± 3	105 ± 3	105 ± 3	105 ± 3
Total cholesterol, mmol/l	6.0 ± 1.1	6.0 ± 1.1	6.2 ± 1.2	6.2 ± 1.2	6.2 ± 1.3	6.1 ± 1.1
Body mass index, kg/m^2	28.4 ± 4.6	28.4 ± 4.6	28.4 ± 4.7	28.6 ± 4.9	28.5 ± 5.3	28.6 ± 4.9
Diabetes mellitus	578 (8)	600 (8)	138 (9)	110 (7)	31 (12)	31 (11)
Previous myocardial infarction	109 (1)	103 (1)	28 (2)	27 (2)	6 (2)	9 (3)
Previous other coronary heart disease	425 (6)	424 (6)	109 (7)	113 (7)	18 (7)	18 (7)
Previous stroke	78 (1)	72 (1)	24 (2)	31 (2)	9 (3)	6 (2)
Current smokers	1,274 (17)	1,282 (17)	160 (10)	168 (11)	39 (15)	30 (11)
History of ACE inhibitor use	1,442 (19)	1,546 (21)	318 (21)	364 (23)	80 (30)	56 (21)
History of beta-blocker use	1,122 (15)	1,114 (15)	247 (16)	222 (14)	40 (15)	41 (15)
History of calcium-channel blocker use	1,637 (22)	1,587 (21)	394 (26)	373 (24)	81 (31)	81 (30)
History of diuretic use	1,225 (16)	1,262 (17)	311 (20)	350 (23)	63 (24)	63 (23)
History of other BP-lowering agent use	410 (5)	407 (5)	97 (6)	90 (6)	22 (8)	27 (10)
History of use of 2+ BP-lowering agents	1,540 (20)	1,583 (21)	377 (25)	412 (26)	83 (31)	81 (30)
Trial assignment						
More intensive BP treatment	2,509 (33)	2,465 (33)	515 (34)	543 (35)	76 (29)	86 (32)
Blood pressure during follow-up, mm Hg						
Systolic BP achieved	142 ± 12	141 ± 12	143 ± 12	142 ± 12	145 ± 14	143 ± 12
Diastolic BP achieved	84 ± 5	83 ± 5	83 ± 5	83 ± 5	83 ± 6	82 ± 6

Values are median (interquartile range), mean ± SD, or n (%).
ACE = angiotensin-converting enzyme; BP = blood pressure; eGFR = estimated glomerular filtration rate.