Background: We examined prospectively which of the four blood pressure (BP) components (systolic BP [SBP], diastolic BP [DBP], pulse pressure [PP], and mean arterial pressure [MAP]) was best in predicting the risk of proteinuria.

Methods: This prospective study included 9341 non-diabetic Japanese middle-aged men who had no proteinuria and an estimated glomerular filtration rate ≥60 mL/min/1.73 m² and were not taking antihypertensive medications at entry. Persistent proteinuria was defined if proteinuria was detected two or more times consecutively and persistently at the annual examination until the end of follow-up. We calculated the difference in values of Akaike’s information criterion (ΔAIC) in comparison of the BP components-added model to the model without them in a Cox proportional hazards model.

Results: During the 84,587 person-years follow-up period, we confirmed 151 cases of persistent proteinuria. In multiple-adjusted models that included a single BP component, the hazard ratios for persistent proteinuria for the highest quartile of SBP, PP, and MAP were 3.11 (95% confidence interval [CI], 1.79–5.39), 1.87 (95% CI, 1.18–2.94), and 2.21 (95% CI, 1.33–3.69) compared with the lowest quartile of SBP, PP, and MAP, respectively. The hazard ratio for the highest quartile of DBP was 2.69 (95% CI, 1.65–4.38) compared with the second quartile of DBP. Of all models that included a single BP component, those that included SBP alone or DBP alone had the highest values of ΔAIC (14.0 and 13.1, respectively) in predicting the risk of persistent proteinuria.

Conclusions: Of all BP components, SBP and DBP were best in predicting the risk of persistent proteinuria in middle-aged Japanese men.

Introduction

Hypertension is a well-established major risk factor for cardiovascular disease. Although the chief criteria for defining hypertension have been based on systolic blood pressure (SBP) and diastolic blood pressure (DBP), it might be important for better prediction to consider two additional blood pressure (BP) components: a pulsatile component, such as pulse pressure (PP), and a steady component, such as mean arterial pressure (MAP). In epidemiological studies that have compared these BP components (SBP, DBP, PP, and MAP) individually as predictors of risk for cardiovascular diseases, SBP or PP has been reported to be associated with coronary heart disease, whereas SBP has been associated with stroke. Hypertension is also associated with the risk of chronic kidney disease, and a few prospective studies have reported the association between various BP components and the decline of glomerular filtration rate. Although proteinuria is a component of...
chronic kidney disease and has been associated with the incidence of cardiovascular disease, end-stage renal disease, and all-cause mortality. It is not known which of the four BP components is best in predicting the risk of incident proteinuria. Only two longitudinal studies have examined the associations between the four BP components and future albuminuria. However, as both studies measured urinary albumin excretion only at the end point of their analytic cohorts, they have not examined the association between these BP components and incident risk of albuminuria. To our knowledge, no prospective cohort study has compared various BP components as predictors of risk for incident proteinuria.

We examined the relation of BP components (SBP, DBP, PP and MAP), both individually and combined, to the risk of the incidence of proteinuria in an 11-year prospective observational study in apparently healthy middle-aged Japanese men. To avoid the influence of subjects with transient proteinuria, we used the definition of persistent proteinuria, which was defined as proteinuria detected two or more times consecutively and persistently at the annual examination until the end of follow-up.

Methods

Study population

The study population was Japanese men enrolled in the Kansai Healthcare Study, which is an ongoing prospective cohort study examining risk factors for cardiometabolic diseases. Between April 2000 and March 2001, 12,647 men aged 40–55 years who were employees of a company in the Kansai area of Japan and who were considered to be involved in sedentary jobs at entry were enrolled in this study. All employees of this company aged 40 years or older have undergone annual medical checkups because Japanese law requires it. When the data based on only the results of or older have undergone annual medical checkups because Japanese law requires it. When the data based on only the results of

Outcome

Proteinuria on urine dipstick examination was defined as 1+ or higher (30 mg/dL or higher) at the annual medical check-up. We used the definition of persistent proteinuria to exclude transient proteinuria: “persistent proteinuria” was defined if proteinuria was detected two or more times consecutively and persistently at the annual examination until the end of follow-up.

Statistical analysis

To assess the difference in baseline characteristics between subjects who developed persistent proteinuria and those who did not, we used the unpaired t-test, Mann–Whitney test, or chi-squared test (Table 1). Multivariate Cox proportional hazards models were used to investigate the association between BP components and the incidence of persistent proteinuria. Follow-up of each subject was continued until the diagnosis of the outcome occurrence or until the 11-year follow-up examination from April 1, 2011 to March 31, 2012, whichever came first. We evaluated nonlinear effects of continuous independent variables using fractional polynomials or by plotting the regression coefficients against the variables. In the Cox proportional hazards models of Table 2, BMI, alcohol consumption, DBP, and MAP did not fulfill the linearity assumption. As the association between BMI and risk of persistent proteinuria was a U-shaped association, the BMI level was classified into seven categories: <18.0, 18.0–19.9, 20.0–21.9, 22.0–23.9, 24.0–25.9, 26.0–27.9, and ≥28.0 kg/m². Regarding drinking habits, except nondrinkers, subjects were classified into tertiles of daily alcohol consumption levels: 0.1–16.4, 16.5–42.7, and ≥42.8 g ethanol/day. Each BP component was categorized by quartile in all models of Tables 2 and 3. Therefore, we included the
Data are presented as mean (standard deviation), median (25th to 75th percentiles), or % and compared using unpaired t-test, Mann-Whitney test, or chi-squared test. * Persistent proteinuria was defined as proteinuria detected two or more times consecutively and persistently at the annual examination until the end of follow-up. ** Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg. *** Daily alcohol consumption was calculated as [(the quantity consumed per drinking day) × (the weekly frequency of alcohol consumption)]/7.

Table 1 reports the baseline characteristics of the subjects by whether or not persistent proteinuria developed during the follow-up period.

|                          | Total (-) | Persistent proteinuria* (+) | P value |
|--------------------------|-----------|-----------------------------|---------|
| Number                   | 9341      | 9190                        | 151     |
| Age, years               | 48.2 (4.2)| 48.2 (4.2)                  | 48.8 (4.0) | 0.074 |
| Body mass index, kg/m²   | 23.2 (2.8)| 23.2 (2.8)                  | 24.4 (3.2) | <0.001 |
| Systolic blood pressure, mm Hg | 127.6 (17.7) | 127.5 (17.6) | 135.5 (19.1) | <0.001 |
| Diastolic blood pressure, mm Hg | 79.7 (11.8) | 79.6 (11.7) | 84.0 (14.7) | <0.001 |
| Pulse pressure, mm Hg    | 47.9 (12.5)| 47.9 (12.4)                  | 51.4 (14.3) | <0.001 |
| Mean arterial pressure, mm Hg | 95.6 (12.7)| 95.5 (12.7) | 101.2 (14.8) | <0.001 |
| Hypertension, %a          | 28.1      | 27.8                        | 48.3    | <0.001 |
| Fasting plasma glucose, mg/dL | 97.2 (9.2) | 97.2 (9.2)                  | 99.5 (9.1) | 0.002 |
| Serum creatinine, mg/dL  | 0.79 (0.11)| 0.79 (0.11)                 | 0.77 (0.12) | 0.015 |
| Estimated glomerular filtration rate, ml/min/1.73 m² | 84.8 (14.1) | 84.8 (14.0) | 87.7 (16.4) | 0.011 |
| Daily alcohol consumption, g ethanol/dayb | 23.0 (3.3–46.0) | 23.0 (3.3–46.0) | 24.6 (8.2–46.0) | 0.214 |
| Drinking habit, %         | 85.0      | 85.1                        | 94.1    | 0.744 |
| Regular leisure-time physical activity, % | 17.9 | 18.0 | 9.3 | 0.005 |
| Smoking habits,c          |          |                             |         |
| Nonsmokers               | 21.2      | 21.2                        | 19.2    |         |
| Past smokers             | 21.6      | 21.7                        | 17.2    | 0.254 |
| Current smokers          | 57.2      | 57.1                        | 63.6    |         |

Results

Table 1 reports the baseline characteristics of the subjects by incident persistent proteinuria status. Subjects who developed persistent proteinuria had higher mean values of SBP, DBP, PP, and MAP than those who did not. The group of subjects who developed persistent proteinuria had a higher proportion of hypertension and higher mean BMI and eGFR at baseline.

During the 84,587 person-years of follow-up period, 151 subjects had persistent proteinuria. The incidence rate and multiple-adjusted hazard ratios are shown in Table 2. In multiple-adjusted models including a single BP component, SBP, DBP, PP, or MAP, higher levels of SBP, PP, and MAP were associated with an increased risk of persistent proteinuria, and the association between DBP and risk of persistent proteinuria was a U-shaped association. When SBP and DBP were included simultaneously in the model, both SBP and DBP were independently associated with an increased risk of persistent proteinuria. Higher levels of SBP were associated with an increased risk of persistent proteinuria, and the association between DBP and risk of persistent proteinuria was a U-shaped association. When PP and MAP were included simultaneously in the model, both PP and MAP were associated with an increased risk of persistent proteinuria, but the association between PP and risk of persistent proteinuria did not reach statistical significance.

We examined which BP component or combined BP component (i.e., SBP, DBP, PP, MAP, SBP + DBP, or PP + MAP) was the best predictor of incident persistent proteinuria. ΔAIC was calculated as the AIC of the model that did not include any BP components minus the AIC of the model that included any one BP component or combined BP component (Table 3). Of all the models that included a single BP component, those that included SBP alone or DBP alone showed the best improvement of goodness of fit for predicting incident persistent proteinuria (ΔAIC 14.0 and 13.1, respectively). On the other hand, PP alone did not show improvement of goodness of fit for predicting incident persistent proteinuria. When we examined which single BP component or combined BP component was the best predictor of incident persistent proteinuria, the model that included SBP + DBP showed the best goodness of fit to predict the incident persistent proteinuria. The model that included PP + MAP was not superior to models that included SBP alone or DBP alone.

Discussion

These prospective data demonstrated that all the BP components (SBP, DBP, PP, and MAP) were associated with an increased risk of persistent proteinuria. Higher levels of SBP, PP, and MAP
were associated with an increased risk of persistent proteinuria. On the other hand, the association between DBP and persistent proteinuria had a U-shaped association. Of all models that included the single BP component, SBP and DBP were best in predicting the risk of persistent proteinuria. Of all models that included the single BP component or combined BP component, the model that included SBP + DBP showed the best goodness of fit to predict the risk of the incident persistent proteinuria. These associations were independent of age, BMI, fasting plasma glucose level, smoking habits, regular leisure-time activity, drinking habits, and eGFR level.

Only two longitudinal studies have shown the relationship between the four BP components and future albuminuria. Farasat et al.24 reported in the Baltimore Longitudinal Study of Aging that PP was the strongest predictor of 24-h urinary albumin excretion in men, and that each BP component was not associated with urinary albumin excretion in women. Although they have used serial BP measurements during 1–22 years (median, 5 years) preceding urinary albumin excretion measurement as an independent variable, they measured urinary albumin excretion only at the end-point of their analytic cohort. Subjects in their study were older than those in our study, as their older age would be expected to lead to higher albuminuria.

Table 2
Comparison of four blood components in predicting the incidence of persistent proteinuria.

| Model                  | Incidence rateb (case/person-years) | Multiple-adjusted hazard ratio (95% CI) | P value |
|------------------------|-------------------------------------|----------------------------------------|---------|
| Base modela = single BP component |                                     |                                         |         |
| SBP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−115)      | 0.83 (18/21617)                     | 1.00 (reference)                       |         |
| Quartile 2 (116–126)   | 1.56 (35/22416)                     | 1.85 (1.04–3.28)                      | 0.036   |
| Quartile 3 (127–138)   | 1.63 (35/21501)                     | 1.77 (0.99–3.17)                      | 0.055   |
| Quartile 4 (139–)      | 3.31 (63/19053)                     | 3.11 (1.79–5.39)                      | <0.001  |
| P for trend            |                                     |                                         | <0.001  |
| DBP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−71)       | 1.52 (33/21689)                     | 1.65 (0.97–2.83)                      | 0.067   |
| Quartile 2 (72–80)     | 1.00 (23/23027)                     | 1.00 (reference)                      |         |
| Quartile 3 (81–87)     | 1.57 (32/20441)                     | 1.44 (0.84–2.47)                      | 0.184   |
| Quartile 4 (88–)       | 3.24 (63/19430)                     | 2.69 (1.65–4.38)                      | <0.001  |
| P for trend            |                                     |                                         |         |
| MAP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−86.7)     | 1.05 (33/21972)                     | 1.00 (reference)                      |         |
| Quartile 2 (86.8–95.0) | 1.49 (32/21437)                     | 1.30 (0.76–2.24)                      | 0.342   |
| Quartile 3 (95.1–103.3)| 1.58 (33/20884)                     | 1.31 (0.75–2.27)                      | 0.339   |
| Quartile 4 (103.4–)    | 3.10 (63/20294)                     | 2.21 (1.33–3.69)                      | 0.002   |
| P for trend            |                                     |                                         |         |
| Base modela = two BP components |                                 |                                         |         |
| SBP and DBP            |                                     |                                         |         |
| SBP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−115)      | 1.00 (reference)                    |                                         |         |
| Quartile 2 (116–126)   | 2.23 (1.22–4.07)                    | 0.009                                 |         |
| Quartile 3 (127–138)   | 2.07 (1.07–3.97)                    | 0.030                                 |         |
| Quartile 4 (139–)      | 3.19 (1.61–6.30)                    | 0.001                                 |         |
| P for trend            |                                     |                                         |         |
| DBP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−71)       | 2.14 (1.23–3.74)                    | 0.007                                 |         |
| Quartile 2 (72–80)     | 1.00 (reference)                    |                                         |         |
| Quartile 3 (81–87)     | 1.24 (0.71–2.15)                    | 0.446                                 |         |
| Quartile 4 (88–)       | 1.94 (1.12–3.34)                    | 0.017                                 |         |
| P for trend            |                                     |                                         |         |
| PP and MAP             |                                     |                                         |         |
| PP, mm Hg              |                                     |                                         |         |
| Quartile 1 (−40)       | 1.00 (reference)                    |                                         |         |
| Quartile 2 (41–47)     | 1.19 (0.72–1.96)                    | 0.493                                 |         |
| Quartile 3 (48–55)     | 1.21 (0.73–1.99)                    | 0.457                                 |         |
| Quartile 4 (56–)       | 1.54 (0.96–2.49)                    | 0.075                                 |         |
| P for trend            |                                     |                                         |         |
| MAP, mm Hg             |                                     |                                         |         |
| Quartile 1 (−86.7)     | 1.00 (reference)                    |                                         |         |
| Quartile 2 (86.8–95.0) | 1.27 (0.74–2.19)                    | 0.390                                 |         |
| Quartile 3 (95.1–103.3)| 1.23 (0.71–2.14)                    | 0.462                                 |         |
| Quartile 4 (103.4–)    | 1.94 (1.14–3.29)                    | 0.015                                 |         |
| P for trend            |                                     |                                         |         |

BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure.

a Persistent proteinuria was defined if proteinuria was detected two or more times consecutively and persistently at the annual examination until the end of follow-up.
b Incidence rates are expressed as the incidence per 1000 person-years.
c Adjusted for base model + single BP component or two BP components.
d Base model included age, body mass index categories (<18.0, 18.0–19.9, 20.0–21.9, 22.0–23.9, 24.0–25.9, 26.0–27.9, ≥28.0), fasting plasma glucose, smoking habits (non-smokers, past smokers, current smokers), regular leisure-time activity (yes or no), drinking habits (non-drinkers, 0.1–16.4, 16.5–42.7, ≥42.8 g ethanol/day), and estimated glomerular filtration rate at baseline.
than our subjects, and PP becomes increasingly greater with advancing age,36,37 which may explain the difference between their results and ours. Tsakiris et al.38 showed in the Three-Areas Study in Greece that SBP, DBP, and MAP at entry were associated with microalbuminuria measured at the end of the 12-year follow-up period. They did not measure urinary albumin excretion at entry, and the follow-up rate was low (57%). As both studies did not assess the presence or absence of albuminuria at entry, they have not examined the relationship between BP components and the incident risk of albuminuria.

One of the strengths of this study was that we examined the association between BP components and incident persistent proteinuria to avoid the influence of subjects with transient proteinuria. Previous studies24,25 on the association between BP components and the risk of albuminuria have used single measurements of urinary albumin excretion.

In this study, we did not identify why SBP and DBP were the best predictors of incident proteinuria. In general, chronic hypertension causes impairment of the renal autoregulation mechanism, which keeps renal blood flow and the glomerular filtration rate constant when blood pressure level increases.39 This impairment leads to glomerular hypertension and an increase in proteinuria.38 Although SBP rises steadily with age, DBP rises until around age 50 and thereafter falls progressively. PP becomes increasingly greater when blood pressure level increases.38 This impairment leads to renal blood flow, and causes impairment of the renal autoregulation mechanism, which keeps renal blood flow and the glomerular filtration rate constant when blood pressure level increases.39 This impairment leads to glomerular hypertension and an increase in proteinuria.38

### Table 3

The effects of adding each BP component to base model in predicting the incidence of persistent proteinuria.

| Model 1                        | Model 2                        | ∆AIC |
|-------------------------------|-------------------------------|------|
| Base model                    | Base model + SBP              | 14.0 |
| Base model                    | Base model + DBP              | 13.1 |
| Base model                    | Base model + PP               | 2.0  |
| Base model                    | Base model + MAP              | 6.4  |
| Base model                    | Base model + SBP + DBP        | 20.0 |
| Base model                    | Base model + PP + MAP         | 3.8  |

AIC, Akaike's information criterion; BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure. We calculated AIC for persistent proteinuria by comparing model 2 to model 1. ∆AIC was used to evaluate which BP components or combined BP components, SBP, DBP, PP, MAP, SBP + DBP or PP + MAP, were superior as the risk for incident persistent proteinuria. Higher value of ∆AIC indicated better model fit. Base model included age, body mass index categories (<18.0, 18.0–19.9, 20.0–21.9, 22.0–23.9, 24.0–25.9, 26.0–27.9, ≥28.0), fasting plasma glucose, smoking habits (non-smokers, past smokers, current smokers), regular leisure-time activity (yes or no), drinking habits (non-drinkers, 0.1–16.4, 16.5–42.7, ≥42.8 g ethanol/day), and estimated glomerular filtration rate at baseline, but no BP component. Model 2 included each BP component quartile in addition to all variables of base model. Persistent proteinuria was defined if proteinuria was detected two or more times consecutively and persistently at the annual examination until the end of follow-up.

### Conflicts of interest

None declared.

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