Effect of Hypertension on Aortic Artery Disease-Related Mortality
— 3.8-Year Nationwide Community-Based Prospective Cohort Study —

Yoichiro Otaki, MD, PhD; Tetsu Watanabe, MD, PhD; Tsuneo Konta, MD, PhD; Masafumi Watanabe, MD, PhD; Shouichi Fujimoto, MD, PhD; Yuji Sato, MD, PhD; Koichi Asahi, MD, PhD; Kunihiro Yamagata, MD, PhD; Kazuhiro Tsuruya, MD, PhD; Ichie Narita, MD, PhD; Masato Kasahara, MD, PhD; Yugo Shibagaki, MD, PhD; Kunitoshi Iseki, MD, PhD; Toshiki Moriyama, MD, PhD; Masahide Kondo, MD, PhD; Tsuyoshi Watanabe, MD, PhD

Background: Aortic artery disease (AAD), such as aortic dissection or aortic aneurysm rupture, is fatal, with an extremely high mortality. Because of its low incidence, the risk for the development of AAD has not yet been elucidated. Hypertension (HT) is an established risk factor for cardiovascular disease, but there has been no prospective study on the effect of HT on AAD-related mortality.

Methods and Results: We used a nationwide database of 276,197 subjects (aged 40–75 years) who participated in the annual “Specific Health Check and Guidance in Japan” from 2008 to 2010. There were 80 AAD-related deaths during the follow-up period of 1,049,549 person-years. On multivariate Cox proportional hazard regression, HT was an independent risk factor for AAD-related death in apparently healthy subjects. On receiver operating characteristics curve analysis for AAD-related death, abnormal systolic and diastolic blood pressure (SBP and DBP) were 130 mmHg and 82 mmHg, respectively. The prediction capacity was significantly improved by the addition of SBP to confounding risk factors. Notably, further improvement of the C index was observed by addition of DBP to the model with SBP.

Conclusions: This is the first report to prospectively show that HT is a risk factor for AAD-related death. Both SBP and DBP are of critical importance in the primary prevention of AAD-related death in apparently healthy subjects.

Key Words: Aortic artery disease-related mortality; Apparently healthy subject; Hypertension

Aortic artery disease (AAD), namely aortic artery dissection or aortic aneurysm rupture, is a major cause of sudden death.12 In almost all cases of aortic aneurysm rupture, the patient dies before arriving at hospital; furthermore, the mortality rate ≤24h after symptom onset reaches approximately 50–70% despite surgical treatment.3 Similarly, the mortality rates in those with ascending aortic dissection between 24 h and 1 month after onset are 20% and 50%, respectively.4 Therefore, it is critical to identify high-risk subjects and prevent the development of AAD in apparently healthy subjects using health check-ups.

The prevalence of hypertension (HT) is still increasing and is a well-known risk for cardiovascular disease and mortality. The mechanisms by which HT is involved in the development of cardiovascular disease includes several complex processes such as the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS), and oxidative stress.5 Several guidelines, such as the Japanese Society of Hypertension (JSH) 2014, recommend lowering blood pressure (BP) to <140 and <90 mmHg for the primary
prevention of cardiovascular disease. There is no evidence, however, concerning the recommended BP lowering level to prevent AAD-related death in apparently healthy subjects because of its relatively lower prevalence compared with cardiovascular disease. In the present study, we therefore examined whether HT could be a pivotal risk factor for AAD-related death in apparently healthy subjects.

Methods

Subjects
This study is part of an ongoing investigation titled “Research on design of the comprehensive health care system for chronic kidney disease (CKD)” based on individual risk assessments by the Specific Health Check-Up for all inhabitants of Japan between the age of 40 and 74 years, and is covered by Japanese National Health Insurance. We utilized data obtained from 16 prefectures involving 55 municipalities (i.e., administrative regions): Hokkaido, Tochigi, Saitama, Chiba, Nagano, Niigata, Ishikawa, Fuku, Gifu, Hyogo, Tokushima, Fukuoka, Saga, Nagasaki, Kumamoto, and Okinawa. These prefectures were divided into 4 region areas: Hokkaido and Tohoku; Kantō and Koshinetsu; Kinki, Shikoku, and Chugoku; and Kyushu and Okinawa. We collected data from 119,788 men and 175,509 women (total, 295,297; age range, 40–74 years) who participated in the health check-ups from 2008 to 2010. Of the 295,297 individuals, 19,100 were excluded from this study because of the lack of essential data including systolic BP (SBP), diastolic BP (DBP) and alcohol consumption. Therefore, a total of 111,095 men and 165,102 women were included in the study.

Definition of Cardiovascular Risk
HT was defined as SBP \( \geq 140 \text{mmHg} \) and DBP \( \geq 90 \text{mmHg} \) or use of antihypertensive medication. Diabetes mellitus (DM) was defined as fasting plasma glucose (FPG) \( \geq 126 \text{mg/dL} \) and glycosylated hemoglobin A1c (HbA1c) \( \geq 6.5\% \) (National Glycohemoglobin Standardization Program), or use of anti-diabetic medication. Dyslipidemia (DL) was defined as high-density lipoprotein cholesterol (HDL-C) \( < 40 \text{mg/dL} \), low-density lipoprotein cholesterol (LDL-C) \( \geq 140 \text{mg/dL} \), and triglycerides \( \geq 150 \text{mg/dL} \) or use of lipid-lowering medication.

BP Measurement
Participants were seated with back support. After resting for \( \geq 5 \) min, BP was measured twice without conversation. BP was determined from an average of 2 BP readings. Mean BP and pulse pressure were measured according to the JSH 2014 guideline: pulse pressure=SBP−DBP; and mean BP=DBP+pulse pressure/3.

Biochemistry
FPG, HbA1c, HDL-C, LDL-C, and triglycerides were measured. Serum creatinine was measured using an enzymatic method, whereas estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation with the Japanese coefficient. All blood analyses were performed at a local laboratory. The methods for the analyses were not standardized between laboratories, but the analyses were based on the Japan Society of Clinical Chemistry recommended methods for laboratory tests, which have been widely accepted by laboratories across Japan.

Endpoint and Follow-up
After obtaining permission from the Ministry of Health, Labour and Welfare, we accessed the database containing death certificates for all deaths that occurred between 2008 and 2012 (total, approximately 6 million). All subjects were prospectively followed up for a period of 1,049,549 person-years. The endpoint was AAD-related death, such as aortic dissection and aortic aneurysmal rupture. The cause of death was determined on review of the death certificates and classified based on the death code (International Classification of Diseases, 10th Revision).

Ethics
All procedures performed in the studies involving human participants were done in accordance with the guidelines of the institutional ethics committee and/or national research committee (Yamagata University, 2008, no. 103) and in compliance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent
This study was performed according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted by the Ministry of Health, Labour and Welfare of Japan (http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf; http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf). In the context of the guidelines, the investigators are not necessarily required to obtain informed consent, but we publicized information concerning this study on the Web (http://www.fmu.ac.jp/univ/sangaku/data/koukai_2/2771.pdf) and ensured that the subjects could refuse the use of their personal information.

Statistical Analysis
Continuous and categorical variables were compared using t-test and chi-square test, respectively. The incidence of AAD-related death was calculated using the person-year method and compared with that in the Japanese demographic statistics data. Survival curves were constructed using the Kaplan-Meier method and compared using log-rank test. Cox proportional hazard analysis was performed to determine independent predictors for AAD-related death, and cardiovascular risk factors and the known risk for AAD-related death were entered into multivariate analysis. Receiver operating characteristic (ROC) curves for AAD-related death were constructed and used as a measure of the predictive accuracy of SBP, DBP, pulse pressure, and mean BP for AAD-related death. We calculated the net reclassification index (NRI) and integrated discrimination index (IDI) to measure the quality of improvement for the correct reclassification by the addition of SBP and DBP to the multivariate model. Differences between the 4 groups were determined using analysis of variance (ANOVA) with Tukey’s post-hoc test. P<0.05 was considered statistically significant. All statistical analysis was performed using JMP version 12 (SAS Institute, Cary, NC, USA), and R 3.0.2 with additional packages including Rcmdr, Epi, pROC, and PredictABEL.

Results
Baseline Characteristics and Presence of HT
Subject baseline characteristics are listed in Table 1. HT,
Hypertension and Aortic Artery Disease

also related to AAD-related mortality. On multivariate Cox proportional hazard regression analysis, HT was an independent predictor of future AAD-related death after adjustment for age, sex, DL, obesity, smoking, alcohol consumption, and region area (HR, 4.354; 95% CI: 2.476–8.203; P<0.0001; Table 2).

Addition of SBP and DBP to Prediction of AAD-Related Mortality

To examine whether model fit and discrimination were improved by the addition of SBP and DBP, we analyzed the ROC curves for AAD-related mortality and calculated NRI and IDI. The baseline model included age, sex, DL, obesity, smoking, alcohol consumption, and region area. To examine whether model fit and discrimination improved with the addition of SBP and DBP to the basic predictors such as age, sex, DL, obesity, smoking, alcohol consumption, and region area, we evaluated the improvement in C index, NRI, and IDI. On ROC curve analysis, the C index of the baseline model was significantly improved by the addition of SBP (Figure 2). NRI and IDI were also significantly improved by the addition of SBP (Table 3).

DL, DM, and obesity were identified in 123,063 (45%), 150,069 (54%), 23,281 (8%), and 75,033 patients (27%), respectively. Mean BP and mean SBP, DBP, and pulse pressure were 94, 129, 76, and 52 mmHg, respectively.

Subjects with HT were older and more likely to be male, had DM and were obese, were smokers, or were taking antihypertensive, anti-diabetic, or anti-dyslipidemic drugs. In addition, subjects with HT had higher triglycerides, LDL-C, FPG, HbA1c, and creatinine and lower HDL-C and eGFR than those without HT (Table 1).

HT and AAD-Related Death

During the follow-up period, a total of 80 AAD-related deaths occurred. The incidence of AAD-related death was 7.6/100,000 person-years. On Kaplan-Meier analysis, subjects with HT had a higher rate of AAD-related death than those without HT (Figure 1).

To determine the risk factors for predicting AAD-related death, we performed univariate and multivariate Cox proportional hazard regression analyses. On univariate analysis, HT was significantly associated with AAD-related mortality (Table 2). Age, male sex, and obesity were also related to AAD-related mortality. On multivariate Cox proportional hazard regression analysis, HT was an independent predictor of future AAD-related death after adjustment for age, sex, DL, obesity, smoking, alcohol consumption, and region area (HR, 4.354; 95% CI: 2.476–8.203; P<0.0001; Table 2).

Addition of SBP and DBP to Prediction of AAD-Related Mortality

To examine whether model fit and discrimination were improved by the addition of SBP and DBP, we analyzed the ROC curves for AAD-related mortality and calculated NRI and IDI. The baseline model included age, sex, DL, obesity, smoking, alcohol consumption, and region area. To examine whether model fit and discrimination improved with the addition of SBP and DBP to the basic predictors such as age, sex, DL, obesity, smoking, alcohol consumption, and region area, we evaluated the improvement in C index, NRI, and IDI. On ROC curve analysis, the C index of the baseline model was significantly improved by the addition of SBP (Figure 2). NRI and IDI were also significantly improved by the addition of SBP (Table 3).
Furthermore, on ROC curve analysis the C index of the baseline model with SBP was significantly improved by the addition of DBP (Figure 2). Similar results were obtained for NRI and IDI (Table 3).

**Abnormal BP Cut-Offs for AAD-Related Mortality**

We determined that HT is a pivotal risk factor for AAD-related mortality in apparently healthy subjects. On ROC curve analysis of BP parameters for AAD-related mortality in apparently healthy subjects, the abnormal cut-offs for SBP and DBP were 130 and 82 mmHg, respectively (Figure 3). In addition, those of mean BP and pulse pressure were 101 and 44 mmHg, respectively.

**Discussion**

The main findings in the present study are as follows: (1) the incidence of AAD-related death was 7.6 per 100,000 person-years; (2) on Kaplan-Meier analysis, subjects with HT had a higher rate of AAD-related death; (3) on multivariate analysis, HT was an independent predictor of AAD-related death; (4) the baseline prediction model was significantly improved by the addition of SBP in apparently healthy subjects.

**Table 2. Predictors of AAD-Related Death (Cox Proportional Hazard Analysis)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P-value</td>
<td>HR 95% CI P-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.092 1.050–1.135 &lt;0.0001</td>
<td>1.078 1.036–1.122 0.0002</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.486 1.591–3.950 &lt;0.0001</td>
<td>1.821 1.074–3.112 0.0258</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.018 3.489–11.161 &lt;0.0001</td>
<td>4.354 2.476–8.203 &lt;0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1.027 0.627–1.516 0.9033</td>
<td>1.181 0.750–1.882 0.4692</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.089 1.031–1.151 0.0021</td>
<td>1.052 0.984–1.124 0.1373</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.700 0.964–2.836 0.0655</td>
<td>1.797 0.989–3.115 0.0541</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>1.529 0.984–2.375 0.0579</td>
<td>1.061 0.643–1.765 0.8173</td>
</tr>
<tr>
<td>Hokkaido and Tohoku†</td>
<td>1.727 0.725–4.168 0.2147</td>
<td>1.402 0.586–3.392 0.4438</td>
</tr>
<tr>
<td>Kinki, Shikoku and Chugoku†</td>
<td>0.296 0.016–1.550 0.1724</td>
<td>0.252 0.014–1.321 0.1149</td>
</tr>
<tr>
<td>Kyushu and Okinawa†</td>
<td>1.327 0.705–2.774 0.3984</td>
<td>1.274 0.677–2.664 0.4723</td>
</tr>
</tbody>
</table>

†vs. Kanto and Koshinetsu. AAD, aortic artery disease.
Hypertension and Aortic Artery Disease

**Table 3. Prediction of AAD-Related Death: Addition of SBP and DBP**

<table>
<thead>
<tr>
<th>Baseline model</th>
<th>NRI (95% CI), P-value</th>
<th>IDI (95% CI), P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
<tr>
<td>+SBP</td>
<td>0.4673 (0.2516–0.6831), &lt;0.0001</td>
<td>0.0002 (0.0001–0.0003), 0.0049</td>
</tr>
<tr>
<td>+SBP+DBP</td>
<td>0.5151 (0.3029–0.7273), &lt;0.0001</td>
<td>0.0003 (0.0001–0.0006), 0.0011</td>
</tr>
</tbody>
</table>

Baseline model includes age, gender, obesity, dyslipidemia, smoking, alcohol consumption and region area. IDI, integrated discrimination index; NRI, net reclassification index. Other abbreviations as in Tables 1,2.

**Figure 3.** Receiver operating characteristic curves of (A) systolic blood pressure (BP), (B) diastolic BP, (C) pulse pressure, and (D) mean BP for aortic artery disease-related death.

Healthy subjects and it was further improved by the addition of DBP; and (5) the abnormal cut-offs for SBP, DBP, pulse pressure, and mean BP estimated using a nationwide cohort were 130, 82, 44, and 101 mmHg, respectively.

**HT and AAD**

According to Japanese demographic statistics in 2016, the incidence of AAD-related deaths was 14.5 per 100,000 person-years. In this study, the incidence of AAD-related deaths calculated using the person-year method was 7.6 per 100,000 person-years. Given that the present study includes an apparently healthy population aged 40–75 years, it was reasonable that the incidence of AAD-related death was lower in the present study than in the Japanese demographic statistics.

The precise mechanism of AAD development has been discussed, and medial degeneration is regarded as a common histological characteristic for AAD and a risk factor for aortic aneurysm rupture and aortic dissection. HT has been reported to induce medial degeneration, as does aging and connective tissue disease. Patients with AAD have also been reported to have higher angiotensin II than those with ischemic heart disease and unruptured aortic aneurysm. The long infusion of angiotensin II in mice reportedly causes medial degeneration through the interleukin-6-dependent pathway. Several experimental studies indicated that angiotensin II initiates aneurysmal rupture and dissection in mice with medial degeneration, that is, aged mice, apolipoprotein E-knockout mice, and lysyl oxidase inhibitor (β-aminopropionitrile monofumarate)-pretreatment mice. Furthermore, Liu et al reported that mineralocorticoid receptor agonist induces aortic aneurysm formation, leading to rupture in the presence of a high salt diet, and that this was reversed by aldosterone.
receptor blockers such as spironolactone and eplerenone.\textsuperscript{15} A clinical study indicated the usefulness of angiotensin-converting enzyme inhibitor in patients with abdominal aortic aneurysm.\textsuperscript{16} Similarly, the usefulness of angiotensin II receptor blockers has been reported in Marfan syndrome.\textsuperscript{17,18} Surprisingly, BP elevation induced by norepinephrine failed to initiate aortic aneurysm and aortic dissection.\textsuperscript{12} Given that RAAS activation and its overactivity lead to atherosclerosis, organ damage, and an increase in reactive oxygen species,\textsuperscript{19,20} it is plausible that HT is associated with the development of AAD through RAAS activation. Further studies are needed to identify the specific mechanism by which HT worsens AAD.

**Abnormal Cut-Off for AAD-Related Death**
There is still room for discussion on the target value of BP-lowering therapy even in the field of cardiovascular disease. The randomized trial of intensive vs. standard BP control (SPRINT trial) demonstrated that intensive SBP control at <120 mmHg reduced the risk of cardiovascular events, superior to standard BP control at <140 mmHg in HT patients without DM.\textsuperscript{21} Similarly, the Hypertension Optimal Treatment (HOT) trial showed that intensive BP lowering reduced the risk of cardiovascular disease in patients with type II DM.\textsuperscript{22} In contrast, the action to control cardiovascular risk in the diabetes BP trial (ACCORD BP trial) demonstrated that this intensive BP control failed to reduce the risk for cardiovascular mortality in HT patients with DM.\textsuperscript{23} The ACC/AHA/ABC/ACPM/AGS/APHA/ASH/ASPC/NMA/PCNA 2017 guidelines redefined HT as SBP >130 or DBP >80 mmHg, and noted that SBP lowering to <130 mmHg reduced the risk for myocardial infarction, stroke, heart failure and major adverse cardiovascular events.\textsuperscript{24} These guidelines, however, did not include data on AAD-related death.

The JSH 2014 guidelines recommended SBP lowering to <120 mmHg for acute aortic dissection and to 135–140 mmHg in chronic aortic dissection, respectively. Controlled SBP/DBP <130/80 mmHg has also been reported to reduce the risk of recurrence of aortic dissection in patients with type B dissection.\textsuperscript{25} In the present study, the abnormal SBP/DBP cut-off for the primary prevention of AAD-related death was 130/82 mmHg. This equaled the target value of BP-lowering therapy in cardiovascular disease. Therefore, the present results raise the possibility that intensive BP control is also important for the prevention of AAD-related death, as well as cardiovascular disease.

**Systolic and Diastolic HT**
Although both SBP and DBP significantly improved the C-index of the baseline model, the C-index of the baseline model with SBP was further improved by the addition of DBP. This confirms the clinical importance of HT in the development of AAD-related death and raises the possibility that DBP could be an additional clinical factor to consider besides SBP in apparently healthy subjects. SBP increases and DBP decreases with aging through aortic artery stiffness.\textsuperscript{26–27} Nonetheless, systolic and diastolic HT were identified in 58,953 individuals (21%) in the apparently healthy subjects. It was beyond the scope of the present study to identify the mechanism by which DBP induced AAD-related death, because this was a prospective observational study. One explanation may be that DBP aggravated aortic wall stress. Alternatively, comorbidities of diastolic HT such as obesity and DL may contribute to AAD-related death. The clinical significance of the present study was that both SBP and DBP were pivotal risk factors for AAD-related death, and that BP-lowering therapy is of critical importance in the prevention of premature AAD-related sudden death in apparently healthy subjects.

**Perspectives**
AAD is one of the major causes of sudden death, indicating the importance of primary prevention. This nationwide prospective cohort has clarified the effect of HT on AAD-related mortality in apparently healthy subjects, and suggests the potential target value of BP-lowering therapy for AAD-related death (SBP/DBP, 130/82 mmHg). Similar to cardiovascular disease, intensive BP-lowering therapy may reduce the risk of AAD-related death in apparently healthy subjects.

**Study Limitations**
The strengths of the present study include its large sample size, prospective follow-up design, and nationwide data source. Therefore, the present results are well generalized and highly reliable. There were some limitations as well, however. First, we assessed BP at only 1 point. Given that SBP increased with aging, several subjects developed HT during the follow-up period. Second, we did not examine AAD development and had no medical data on surgical and endovascular aortic repair. Although AAD can be fatal, some subjects survived, most likely because of treatment. Thus, we underestimated the effect of HT on the development of AAD. Third, there was a small number of AAD-related deaths. Fourth, although BP were mainly measured using mercury sphygmomanometer, there was no standardization or inspection system to measure BP in this study. Fifth, we had no data on passive smoking, which is also associated with aortic disease mortality.\textsuperscript{28} Finally, we had no information on the medication used by this population.

**Conclusions**
HT is a pivotal risk factor for AAD-related death in apparently healthy subjects. The abnormal SBP and DBP cut-offs were similar to those for cardiovascular disease. HT, both systolic and diastolic, could be a therapeutic target in the prevention of sudden AAD-related death.

**Acknowledgments**
This work was supported by a Health and Labor Sciences Research Grant for Study on the design of the comprehensive health care system for CKD based on the individual risk assessment by Specific Health Check-Up of the Ministry of Health, Labour and Welfare of Japan and a Grant-in-Aid for Research on Advanced Chronic Kidney Disease (REACH-J), Practical Research Project for Renal Disease Japan and a Grant-in-Aid for Research on Advanced Chronic Kidney Disease (REACH-J), Practical Research Project for Renal Disease (Japan Agency for Medical Research and Development (AMED)).

**Disclosures**
The authors declare no conflicts of interest.

**References**


