Mild Hypertensive Retinopathy and Risk of Cardiovascular Disease: The Suita Study

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Aims: This study aimed to investigate the association of mild hypertensive retinopathy with cardiovascular disease (CVD) risk.

Methods: A total of 7,027 residents aged 30–79 years without a history of CVD participated in the annual health checkups and retinal photography assessments. Retinal microvascular abnormalities were graded using the standard protocols and classified according to the Keith–Wagener–Barker classification. Mild hypertensive retinopathy was defined as grades 1 and 2. Cox proportional hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for total CVD and its subtypes according to the presence and absence of mild hypertensive retinopathy.

Results: During a median follow-up of 17 years, 351 incident stroke and 247 coronary heart disease (CHD) cases were diagnosed. After adjustment for traditional cardiovascular risk factors, mild hypertensive retinopathy was positively associated with risk of CVD (multivariable HR = 1.24; 95% CI, 1.04–1.49) and stroke (1.28; 1.01–1.62) but not with risk of CHD (1.19; 0.89–1.58). Generalized arteriolar narrowing and enhanced arteriolar wall reflex were positively associated with CVD risk, the multivariable HR (95% CI) was 1.24 (1.00–1.54) and 1.33 (1.02–1.74), respectively. Moreover, mild hypertensive retinopathy was positively associated with stroke risk in normotensive participants.

Conclusion: Mild hypertensive retinopathy was positively associated with CVD and stroke risk in the urban Japanese population. Especially, generalized arteriolar narrowing and enhanced arteriolar wall reflex were positively associated with CVD risk. These findings suggested that retinal photography could be helpful for cardiovascular risk stratification in the primary cardiovascular prevention.

Key words: Retinal photography, The Keith–Wagener–Barker classification, Stroke, Coronary heart disease, Follow-up study

Introduction

Retinal photography is a simple, noninvasive approach to evaluate the microvascular health status. Growing evidence from Western studies showed the clinical practice values of retinal microvascular abnormalities on the cardiovascular risk classification1, 2). Retinal microvascular abnormalities are considered as measured surrogates that reflect the development of aging, hypertension, and other vascular diseases3, 5). Current clinical guidelines recommend closely monitoring of cardiovascular risk for participants with
Follow-Up and Ascertainment of Cases

Participants were followed up to (1) the date of the first diagnosed stroke or CHD; (2) the date of death; (3) the date of movement from Suita city; or (4) December 31, 2013. A total of 1,419 (20.2%) participants moved out, and 1,520 (21.6%) died during the follow-up. The follow-up was censored when participants had an incident stroke or CHD, left the city, or died. The median follow-up was 16.7 years.

The CVD surveillance included two paths. First, participants were invited to participate in health checkups every 2 years. Second, questionnaires by mail or telephone were performed every year. Medical records were reviewed and confirmed by registered hospital physicians or research physicians. Stroke was diagnosed, referring to the US National Survey of Stroke criteria, which defined stroke as rapid onset neurological deficits lasting at least 24 h or until death\(^\text{13}\). Stroke subtypes, including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, were diagnosed on the basis of computed tomography, magnetic resonance imaging, or autopsy. Definitive and probable myocardial infarctions were diagnosed according to electrocardiographic examinations, cardiac enzyme elevations, or autopsy, abiding by the criteria of monitoring trends and determinants in cardiovascular disease (MONICA) project\(^\text{14}\). CHD was defined as the initial case of definitive or probable myocardial infarctions, sudden death from the unknown origin within 24 h after onset, or coronary artery disease after percutaneous coronary intervention. CVD was defined as the initial incident case of either stroke or CHD.

Methods

Study Population

This study is a population-based cardiovascular disease study in Suita, located in northern Osaka Prefecture, Japan\(^\text{11, 12}\). Residents aged 30–79 years were randomly selected from the municipality population registry stratified by sex and age groups of 10 year stratum, and 8,360 men and women underwent health checkups at the National Cerebral and Cardiovascular Center. These participants were enrolled from the original cohort between 1989 and 1996, the secondary cohort between 1996 and 1998, and a volunteer group between 1992 and 2006. We excluded 1,333 participants who had histories of stroke or CHD, moved to other communities before the baseline survey, and participants without data on retinal photography, leaving a total of 7,027 participants for this analysis. Most participants (6,083; 86.6% of 7,027) were enrolled from the original cohort. Informed consent was obtained from all study participants, and the institutional review board approved this study of the National Cerebral and Cardiovascular Center (M17–001).

Measurement of Retinal Microvascular Abnormalities and Covariates

A trained medical technologist took nonmydriatic retinal photographs of both the right and left eyes at baseline. Two trained physicians...
independently evaluated retinal photographs taken on the slide photographs and consulted ophthalmologists when needed. Blood pressure and glucose from the medical examination were masked. Retinal microvascular abnormalities consist of generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, and enhanced arteriolar wall reflex. Generalized arteriolar narrowing was graded if most central arteriolar diameters were markedly narrow than neighboring venues. Focal arteriolar narrowing was graded if there were one or more localized constrictions of vessel segments. Arteriovenous nicking was graded if there were disconnected, disappeared, or invisible vein segments on both sides of its crossing under the arteriole. Enhanced arteriolar light reflex was graded if there was a light reflex on the surface of the arteriolar wall\(^1\). These retinopathy signs were summarized using the Keith–Wagener–Barker classification\(^1\), and mild hypertensive retinopathy was defined as grades 1 and 2, with no grade 3 or more being observed.

After at least 5 min of rest, systolic and diastolic blood pressure were measured in a seated position by well-trained physicians using a mercury sphygmomanometer and suitable cuff according to standard protocols. Blood pressure was recorded three times with a 1 min interval, and the mean value of the second and third measurements was adopted. Body mass index was calculated as weight (kg) divided by height (m\(^2\)). Blood tests were performed, including serum total cholesterol, high-density lipoprotein cholesterol, and glucose. Lifestyles such as smoking, drinking, and medication use were asked about using the standard format. Glucose categories were defined as diabetes mellitus (fasting plasma glucose levels \(\geq 126\) mg/dL, non-FPG \(\geq 200\) mg/dL, or use of diabetes mellitus medication), impairment of fasting glucose (FPG 100–125 mg/dL or non-FPG 140–199 mg/dL), and normal glucose tolerance (FPG <100 mg/dL or non-FPG <140 mg/dL). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation modified by the Japanese coefficient (0.881)\(^1\):\(^2\)

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eGFR = 0.881 \times 186 \times \text{age}^{-0.203} \times (\text{serum creatinine})^{-1.154} \times 0.742 \text{ for women}
\]

The standard 12-lead electrocardiogram was obtained from all participants in the supine position, and two well-trained physicians independently coded each record using the Minnesota Code. Atrial fibrillation was defined as 8–3–1 to 8–3–4, and left ventricular hypertrophy was defined as both 3–1 and major ST-T changes abnormality (i.e., 4–1, 4–2, 5–1, or 5–2).

**Statistical Analysis**

Analysis of variance was used to compare the mean values or the proportion of baseline characteristics. Cox proportional hazard regression model was used to calculate the hazard ratios (HRs) with 95% confidence intervals (CIs) according to the presence of mild hypertensive retinopathy referred to the absence. Potential confounding factors were deduced from the cardiovascular risk prediction model “Suita risk score”\(^1\), including age (30–39, 40–49, 50–59, 60–64, 65–69, 70–74, and 75–79 years), sex (male or female), body mass index (<18.5, 18.5–24.9, or \(\geq 25.0\) kg/m\(^2\)), systolic blood pressure (mmHg), antihypertensive medication use (no or yes), total cholesterol levels (<160, 160–239, 240–279, or \(\geq 280\) mg/dL), high-density lipoprotein cholesterol levels (<35, 35–49, 50–59, or \(\geq 60\) mg/dL), antihyperlipidemic medication use (no or yes), atrial fibrillation (no or yes), antiarrhythmic medication use (no or yes), left ventricular hypertrophy (no or yes), diabetes mellitus (no or yes), current smoking (no or yes), and excessive drinking (no or current alcohol intake \(\geq 46\) g/day equivalent to ethanol). Of 2,121 hypertensive participants, 1,275 (60.1%) reported the age of incident hypertension. We further adjusted the duration of hypertension as a dummy variable. Additionally, we analyzed the associations stratified by hypertensive status (normotensive participants, hypertensive participants with controlled blood pressure, and hypertensive participants with uncontrolled blood pressure), and the results are shown in the Supplemental Table 1. Controlled blood pressure in hypertensive participants was defined as systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg with antihypertensive treatments, and uncontrolled blood pressure was defined as systolic blood pressure \(\geq 140\) mmHg or diastolic blood pressure \(\geq 90\) mmHg with or without antihypertensive treatments. All analyses were performed with SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC, USA).

**Results**

Table 1 lists the baseline characteristics of participants according to the Keith-Wagener-Barker grading system. The prevalence of hypertension was 30.2% in the baseline population. The proportion of participants who had hypertensive retinopathy grades 1 and 2 was 19.6% and 0.7%, respectively. Participants with mild hypertensive retinopathy were older and more frequently men than those without.
Table 1. Baseline characteristics of participants according to the Keith-Wagener-Barker classification

|                                      | Normal          | Grades 1 and 2 | P for difference |
|--------------------------------------|-----------------|----------------|------------------|
| No. at risks                         | 5,601           | 1,426          |                  |
| Proportion, %                        | 79.7            | 20.3           |                  |
| Age, year                            | 52.8 (0.2)      | 60.2 (0.3)     | < 0.001          |
| Men, %                               | 45.7            | 49.2           | 0.02             |
| Body mass index, kg/m²               | 22.4 (0.0)      | 23.2 (0.1)     | < 0.001          |
| Systolic blood pressure, mmHg        | 123.4 (0.2)     | 137.0 (0.5)    | < 0.001          |
| Diastolic blood pressure, mmHg       | 76.4 (0.2)      | 83.4 (0.3)     | < 0.001          |
| Antihypertensive medication use, %   | 6.8             | 25.7           | < 0.001          |
| Serum total cholesterol, mg/dL       | 206.9 (0.5)     | 208.6 (1.0)    | 0.12             |
| Serum HDL cholesterol, mg/dL         | 54.7 (0.2)      | 53.4 (0.4)     | 0.001            |
| Antihyperlipidemic medication use, % | 2.0             | 3.0            | 0.03             |
| Atrial fibrillation, %               | 0.8             | 0.4            | 0.16             |
| Antiarrhythmic medication use, %     | 0.2             | 0.1            | 0.65             |
| Left ventricular hypertrophy, %      | 13.6            | 20.8           | < 0.001          |
| eGFR, mL/min/1.73 m²                 | 92.6 (0.4)      | 92.1 (0.8)     | 0.52             |
| Impairment of fasting glucose, %     | 24.7            | 28.6           | 0.003            |
| Diabetes mellitus, %                 | 4.4             | 6.0            | 0.01             |
| Current smokers, %                   | 29.6            | 29.2           | 0.74             |
| Excessive drinking, %                | 14.6            | 16.5           | 0.06             |

Abbreviations: eGFR, estimated glomerular filtration rate.
Values were presented as means (standard errors) or proportion, adjusted for age and sex.

Table 2. Hazard ratios and 95% confidence intervals for total cardiovascular disease, stroke, and coronary heart disease according to the presence and absence of mild hypertensive retinopathy based on the Keith-Wagener-Barker classification

|                                      | Mild hypertensive retinopathy |          |          |
|--------------------------------------|-------------------------------|----------|----------|
|                                      | Absent                        | Present  |          |
| No. at risk                          | 5,601                         | 1,426    |          |
| Person-years                         | 85,983                        | 19,784   |          |
| Total cardiovascular disease         |                               |          |          |
| No. of events                        | 390                           | 208      |          |
| Incident rate, per 1,000 person-years| 4.54                          | 10.51    |          |
| Age- and sex-adjusted HR (95% CI)   | 1.00 (Ref.)                   | 1.59 (1.34–1.89) |          |
| Multivariable-adjusted HR (95% CI)  | 1.00 (Ref.)                   | 1.24 (1.04–1.49) |          |
| Stroke                               |                               |          |          |
| No. of events                        | 228                           | 123      |          |
| Incident rate, per 1,000 person-years| 2.65                          | 6.22     |          |
| Age- and sex-adjusted HR (95% CI)   | 1.00 (Ref.)                   | 1.57 (1.25–1.96) |          |
| Multivariable-adjusted HR (95% CI)  | 1.00 (Ref.)                   | 1.28 (1.01–1.62) |          |
| Coronary heart disease               |                               |          |          |
| No. of events                        | 162                           | 85       |          |
| Incident rate, per 1,000 person-years| 1.88                          | 4.30     |          |
| Age- and sex-adjusted HR (95% CI)   | 1.00 (Ref.)                   | 1.63 (1.25–2.13) |          |
| Multivariable-adjusted HR (95% CI)  | 1.00 (Ref.)                   | 1.19 (0.89–1.58) |          |

Abbreviations: HR, hazard ratio; CI, confidence interval.
Multivariable-adjusted HRs were further adjusted for body mass index, systolic blood pressure, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, antihyperlipidemic medication use, atrial fibrillation, antiarrhythmic medication use, left ventricular hypertrophy, estimated glomerular filtration rate, impairment of fasting glucose, diabetes mellitus, current smoking, and excessive drinking.
HR (95% CI) was 1.24 (1.00–1.54) for generalized arteriolar narrowing and 1.33 (1.02–1.74) for enhanced arteriolar wall reflex. No association was observed for other specific retinal microvascular abnormalities.

Hypertensive status-stratified results are shown in Supplemental Table 1. Mild hypertensive retinopathy tended to be associated with a higher risk of total CVD in hypertensive participants with uncontrolled blood pressure: the multivariable HR (95% CI) was 1.23 (0.97–1.56). Similar trends were observed for stroke and CHD. Furthermore, mild hypertensive retinopathy was associated with a higher risk of stroke in normotensive participants; the multivariable HR (95% CI) was 1.48 (1.01–2.18).

**Discussion**

The present study provided data on the prognostic value of mild hypertensive retinopathy for CVD risk in an urban Japanese population. To our best knowledge, this is the first study to investigate these associations in an urban Japanese population. In previous Japanese studies investigating the association of hypertensive retinopathy and total CVD risk, the prevalence of hypertension was more than 48% 8, 10, whereas the prevalence of hypertension in our study was 30.2%. Moreover, baseline blood pressure levels in our study were closer to the Atherosclerosis Risk in Communities (ARIC) Study, whereas were lower than previous Japanese studies 8, 10. We demonstrated that mild hypertensive retinopathy was positively associated with risk of total CVD and stroke, and generalized arteriolar narrowing and enhanced arteriolar wall

**Table 3.** Hazard ratios and 95% confidence intervals for total cardiovascular disease according to the presence and absence of specific retinal microvascular abnormalities

| Retinal Microvascular Abnormality | Person-years | No. of events | Incident rate, per 1,000 person-years | Age- and sex-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI) |
|---------------------------------|--------------|---------------|--------------------------------------|---------------------------------|-----------------------------------|
| Generalized arteriolar narrowing | Absent       | 93,762        | 449                                  | 4.79                            | 1.00 (Ref.)                        |
|                                 | Present      | 12,004        | 149                                  | 12.41                           | 1.24 (1.00–1.54)                   |
| Focal arteriolar narrowing      | Absent       | 104,060       | 576                                  | 5.54                            | 1.00 (Ref.)                        |
|                                 | Present      | 1,706         | 22                                   | 12.90                           | 1.40 (0.92–2.15)                   |
| Arteriovenous nicking           | Absent       | 96,570        | 513                                  | 5.31                            | 1.00 (Ref.)                        |
|                                 | Present      | 9,196         | 85                                   | 9.24                            | 1.26 (1.00–1.59)                   |
| Enhanced arteriolar wall reflex | Absent       | 100,610       | 537                                  | 5.34                            | 1.00 (Ref.)                        |
|                                 | Present      | 5,157         | 61                                   | 11.83                           | 1.55 (1.19–2.02)                   |

Abbreviations and multivariable adjustment were consistent with Table 2.
reflex were positively associated with risk of total CVD. Additionally, mild hypertensive retinopathy was positively associated with stroke risk in normotensive participants. Our findings support the perspective that retinal microvascular changes could provide positive help for the cardiovascular risk classification.

The positive associations of mild hypertensive retinopathy with total CVD and stroke risk in our study confirmed and expanded the findings from previous studies. In the Ibaraki Prefectural Health Study, the prevalence of mild hypertensive retinopathy was 18.3% for grade 1 and 4.1% for grade 2, and mild hypertensive retinopathy based on the Keith-Wagener-Barker classification was associated with mortalities of total CVD and stroke but not of CHD^{24}. Compared with that study, our study had a higher prevalence of grade 1 and a lower prevalence of grade 2, and observed consistent associations with total CVD and stroke risks. Also, the Ibaraki Prefectural Health Study reported that mild hypertensive retinopathy was associated with mortalities of total CVD and stroke in both participants with and without hypertension, which was similar to our hypertensive status-stratified results.

In the ARIC Study, mild hypertensive retinopathy was positively associated with a 1.96 (1.09–3.55) times higher risk of ischemic stroke in hypertensive participants with medication use and good control of blood pressure at baseline and a 2.29 (1.15–4.54) times higher risk in those with always good control of blood pressure during a 6-year follow-up^{25}. However, our study observed a positive trend in hypertensive participants who had uncontrolled blood pressure but not in hypertensive participants who had controlled blood pressure, suggesting the protective impact of blood pressure control on decreased CVD risk. As for specific retinal microvascular abnormalities, data from the ARIC Study showed the positive associations of retinal hemorrhages, soft exudates, and arteriovenous nicking with risk of stroke^{11} and the positive association of arteriolar narrowing with risk of CHD^{26}. To note, these data came from early analyses with a concise follow-up (3.5 years). The Rotterdam Study reported a positive association of generalized arteriolar narrowing with stroke risk during an 8.5 year follow-up^{19}. Furthermore, a nest case–control study from the Beaver Dam Eye Study reported similar findings that generalized arteriolar narrowing was positively associated with mortality of total CVD^{20}. To our knowledge, no previous study assessed the association of enhanced arteriolar wall reflex with CVD risk. Our finding that enhanced arteriolar wall reflex was positively associated with CVD risk is supported by the Funagata Study^{21}. In that study, enhanced arteriolar wall reflex was positively associated with aging and increased blood pressure levels, suggesting the plausibility that enhanced arteriolar wall reflex could be a predictor of CVD risk.

The retina is the epitome of systemic microcirculation. Retinal and cerebral microvasculature share common embryologic origins, anatomic features, and similar vascularization patterns^{10}. Retinal microvascular abnormalities are generally considered to reflect accumulative vascular damages from aging, hypertension, and other vascular diseases^{3-5}. Generalized arteriolar narrowing is the manifestation of an early stage of hypertensive retinopathy. Elevated blood pressure increases luminal pressure and activates the autoregulatory mechanism, accounting for arteriolar narrowing and vasospasm and, hence, linked to CVD and stroke incidence. The long-term compression of venules causes arteriovenous nicking and enhanced arteriolar wall reflex within the joint adventitial sheath due to elevated blood pressure, which seems to reflect cumulative damages in the cerebral microcirculation more. Several population-based studies reported that retinal microvascular abnormalities were positively associated with past or current blood pressures or both of them^{22, 23}. Furthermore, some retinal microvascular abnormalities were associated with subclinical markers of atherosclerosis and inflammation^{20}.

The strengths of our study come from the cohort characteristics and statistical adjustment. First, the cohort members were randomly enrolled from the population registry with stratified sex and age groups. Second, this is a representative cohort study from the urban Japanese population, which comprises >70% of the national population. The baseline participation rate was 51.4%, and this cohort is the only Japanese cohort composed entirely of an urban population. Third, adjustment variables in the multivariable model were chosen from the Suita risk score, which is a cardiovascular risk prediction model with good predictability^{18}. Fourth, the retinal assessment was performed by a quick screening without pharmacological dilation, so that our findings are likely to be able to be extrapolated to primary prevention in the general population. However, this study had several limitations. First, retinal microvascular abnormalities assessments performed from visual inspection by graders, other than a computer-assisted quantitative approach^{25}, could likely have comparatively poor reproducibility and underestimated these associations. Second, no test data on intergrader and intragrader variability were recorded. Third, the impacts of hypertension and
diabetes on the associations could be substantial. We used single blood pressure and glucose measurement, which cannot wholly exclude their changes during the follow-up. Fourth, the number of CVD subtype cases of some retinal signs could be too small to obtain enough statistical power, so we did not show the associations of specific retinal signs with risk of stroke and CHD. Fifth, we could not provide the specific results of grades 1 and 2 because the number of those cases was small. Finally, residual confounding cannot be ruled out because of the observational study design.

In conclusion, we found that mild hypertensive retinopathy was positively associated with total CVD and stroke risk, and generalized arteriolar narrowing and enhanced arteriolar wall reflex were positively associated with risk of total CVD in the urban Japanese population. Furthermore, mild hypertensive retinopathy was positively associated with stroke risk in normotensive participants. The data support the finding of previous studies that mild hypertensive retinopathy has prognostic value for CVD, and retinal photography is helpful for cardiovascular risk stratification in primary cardiovascular prevention.

Acknowledgements

We would like to thank Dr. Kawanishi and Dr. Misaki, the former and current presidents of the Suita Medical Association, respectively, the members of Suita City Health Center, and the society of the Suita study. We would like to express our special gratitude to Professor Iso from Osaka University. We thank all researchers and staff of the Department of Preventive Cardiology and Department of Preventive Healthcare for performing the medical examinations and follow-ups.

Sources of Funding

This study was supported by the Intramural Research Fund (20-4-9) for the cardiovascular diseases of the National Cerebral and Cardiovascular Center, JST Grant Number JPMJPF2018, and by Health and Labour Sciences Research Grants of the Ministry of Health, Labour and Welfare of Japan (20FA1002). This study was also supported by the Meiji Yasuda Research Institute, Inc. and Meiji Yasuda Life Insurance Company.

Disclosures

None.

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**Supplemental Table 1.** Hazard ratios and 95% confidence intervals according to the presence and absence of mild hypertensive retinopathy, stratified by hypertensive status

|                                | Normotensive participants | Hypertensive participants with controlled blood pressure<sup>a</sup> | Hypertensive participants with uncontrolled blood pressure<sup>b</sup> |
|--------------------------------|---------------------------|-------------------------------------------------|--------------------------------------------------|
|                                | Absent | Present | Absent | Present | Absent | Present |
| No. at risk                    | 4,387  | 519     | 92     | 86      | 1,122  | 821     |
| Person-years                   | 69,253 | 7,777   | 1,122  | 1,063   | 15,607 | 10,944  |
| Total cardiovascular disease   |        |         |        |         |        |         |
| No. of events                  | 228    | 52      | 12     | 12      | 150    | 144     |
| Incident rate, per 1,000 person-years | 3.29  | 6.69    | 10.70  | 11.29   | 9.61   | 13.16   |
| Age- and sex-adjusted HR (95% CI) | 1.00 (Ref.) | 1.38 (1.02–1.87) | 1.00 (Ref.) | 0.99 (0.44–2.23) | 1.00 (Ref.) | 1.31 (1.04–1.65) |
| Multivariable-adjusted HR (95% CI) | 1.00 (Ref.) | 1.26 (0.92–1.72) | 1.00 (Ref.) | 1.15 (0.46–2.87) | 1.00 (Ref.) | 1.23 (0.97–1.56) |
| Stroke                         |        |         |        |         |        |         |
| No. of events                  | 134    | 35      | 9      | 5       | 85     | 83      |
| Incident rate, per 1,000 person-years | 1.93  | 4.50    | 8.02   | 4.70    | 5.45   | 7.58    |
| Age- and sex-adjusted HR (95% CI) | 1.00 (Ref.) | 1.53 (1.05–2.22) | 1.00 (Ref.) | 0.55 (0.18–1.69) | 1.00 (Ref.) | 1.35 (0.99–1.82) |
| Multivariable-adjusted HR (95% CI) | 1.00 (Ref.) | 1.48 (1.01–2.18) | 1.00 (Ref.) | 0.93 (0.22–3.87) | 1.00 (Ref.) | 1.22 (0.89–1.67) |
| Coronary heart disease         |        |         |        |         |        |         |
| No. of events                  | 94     | 17      | 3      | 7       | 65     | 61      |
| Incident rate, per 1,000 person-years | 1.36  | 2.19    | 2.67   | 6.59    | 4.16   | 5.57    |
| Age- and sex-adjusted HR (95% CI) | 1.00 (Ref.) | 1.13 (0.67–1.91) | 1.00 (Ref.) – | 1.00 (Ref.) | 1.27 (0.90–1.81) |
| Multivariable-adjusted HR (95% CI) | 1.00 (Ref.) | 0.96 (0.57–1.63) | 1.00 (Ref.) – | 1.00 (Ref.) | 1.21 (0.84–1.74) |

Abbreviations: HR, hazard ratio; CI, confidence interval.

Multivariable-adjusted HRs were further adjusted for body mass index, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, antihyperlipidemic medication use, atrial fibrillation, antiarrhythmic medication use, left ventricular hypertrophy, estimated glomerular filtration rate, impairment of fasting glucose, diabetes mellitus, current smoking, excessive drinking, and for hypertensive participants with uncontrolled blood pressure, antihypertensive medication use.

<sup>a</sup>Controlled blood pressure was defined as systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg in treated hypertensive participants.

<sup>b</sup>Uncontrolled blood pressure was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in treated or untreated hypertensive participants.