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Association between retinal vein occlusion and early-stage hypertension: A propensity score analysis using a large claims database

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BACKGROUNDS/OBJECTIVES: The threshold of hypertension was lowered from systolic blood pressure (SBP)/diastolic blood pressure (DBP) 140/90 mmHg to 130/80 mmHg by the 2017 American College of Cardiology/American Heart Association blood pressure (BP) guideline. Thus, we investigated the association between retinal vein occlusion (RVO) occurrence and early-stage hypertension.

SUBJECTS/METHODS: This retrospective cohort study used the JMDC Claims Database (JMDC Inc., Tokyo, Japan) between 2005 and 2020. Individuals undergoing health checkups who had data on BP and did not take antihypertensive medications were included. They were classified into four BP groups: normal BP (SBP < 120 mmHg and DBP < 80 mmHg), elevated BP (SBP 120–129 mmHg and DBP < 80 mmHg), stage 1 hypertension (SBP 130–139 mmHg or DBP 80–89 mmHg), and stage 2 hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). Date of RVO occurrence was defined as the first date of diagnosis. We estimated adjusted hazard ratios for RVO and central RVO using weighted Cox regression to adjust for potential confounders.

RESULTS: A total of 2,703,264 individuals were eligible. During a mean follow-up of 1,091 days, 3,526 RVO and 828 central RVO events occurred. The adjusted hazard ratios (95% confidence intervals) were 1.37 (1.19–1.57), 1.95 (1.75–2.18), and 3.33 (2.95–3.76) for RVO and 1.44 (1.07–1.93), 2.17 (1.72–2.73), and 3.76 (2.91–4.86) for central RVO in the elevated BP, stage 1 hypertension, and stage 2 hypertension groups, respectively, compared with the normal BP group.

CONCLUSIONS: Even individuals with early-stage hypertension showed higher risks for RVO and central RVO than individuals with normal BP.

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INTRODUCTION

Retinal vein occlusion (RVO) is one of the most common causes of visual loss [1]. In a meta-analysis performed in 2010, the age- and sex-standardised prevalence of any RVO was 5.20/1,000 population (0.80/1,000 for central RVO) [2], corresponding to more than 40 million people when projected to the world population in 2021 [3]. Although the prognosis of RVO has improved since the appearance of intravitreal ranibizumab and aflibercept [4–8], these drugs are expensive and confer a burden on medical budgets [9]. Furthermore, the prognosis of central RVO remains limited compared with that of branch RVO [6]. Thus, it is important to prevent RVO before its onset.

One of the major and modifiable risk factors for RVO is hypertension [1, 2, 10–13]. The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) blood pressure (BP) guideline defined elevated BP as systolic BP (SBP) 120–129 mmHg and diastolic BP (DBP) < 80 mmHg, and stage 1 hypertension as SBP 130–139 mmHg or DBP 80–89 mmHg [14]. The BP threshold for hypertension was lowered from SBP/DBP ≥ 140/90 mmHg to SBP/DBP ≥ 130/80 mmHg by these new definitions. Previous studies investigated the association between RVO and hypertension using the old definition of hypertension (SBP/DBP ≥ 140/90 mmHg) [11–13]. However, there is little data on whether elevated BP and stage 1 hypertension have specifically higher risks for RVO occurrence compared with normal BP. If such associations are shown, the validity of the 2017 ACC/AHA BP guideline would improve, and the information would be valuable for not only ophthalmologists but also internists.

Therefore, using a large administrative claims database in Japan, we aimed to determine the associations between RVO occurrence and hypertension groups defined by the ACC/AHA guideline, especially whether elevated BP and stage 1 hypertension have higher risks for RVO development than normal BP (SBP/DBP ≤ 120/80 mmHg). We also assessed the proportions of RVO events that would be potentially preventable if elevated BP and stage 1 hypertension were reduced to normal BP using population attributable fractions [15].

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SUBJECTS AND METHODS

Data source

This was a retrospective cohort study using data from the JMDC Claims Database (JMDC Inc., Tokyo, Japan) from 2005 to 2020 [16]. The database collects health insurance claims data from multiple insurance associations and the cumulative number of subjects was approximately 7.3 million in April 2020 [17]. De-identified and individual-level data for both outpatients and inpatients are stored. A strength of the database is that we were able to perform patient-based tracking of visits and treatment flows even if the individual was transferred to another hospital during treatment. The information included was as follows: 1) unique identifier; 2) patient characteristics (age and sex); 3) diagnoses based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes and diagnoses more-finely classified by Japanese text codes; 4) procedures; 5) drugs dispensed based on the Anatomical Therapeutic Chemical Classification System; 6) period from start to end of insurance; and 7) workplace employee annual health checkup data. The checkup data included numerical data, such as body mass index, SBP, DBP, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglycerides, and fasting blood sugar, and self-reported health questionnaire data, such as medical history (cerebrovascular disease, cardiovascular disease, renal failure/dialysis), smoking status (current smoker, ex-/non-smoker), alcohol consumption (daily, sometimes, rarely), and medication use (for hypertension, diabetes mellitus, dyslipidaemia). Because the individuals included in the JMDC database are company employees and their families, the database contains only a small number of individuals aged > 65 years and no individuals aged > 75 years [16]. The present study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of The University of Tokyo. The need for informed consent was waived because of the anonymous nature of the database.

Patient selection

First, we identified individuals who underwent workplace employee annual health checkups and had look-back periods of ≥1 year. This look-back period was set to exclude prevalent cases of RVO. We defined the date of the first health checkup as the index date for each individual. Next, we excluded the individuals with missing data on BP and those taking antihypertensive medications. Furthermore, we excluded those with a history of cardiovascular disease [18], cerebrovascular disease [12, 19], renal failure/dialysis [11, 20], and/or hypercoagulable state [21] at the index date, because these diseases have been shown to be associated with RVO and they can be regarded as distinct populations. Those with missing data on the history of these diseases were also excluded. We excluded individuals who had experienced RVO before the index date (prevalent cases). Finally, we excluded data concerning health checkups that were performed outside of an individual's observation period. Follow-up of patients started at the index date and ended at the date of RVO occurrence or last date of data collection. The study design is shown in Supplementary Fig. 1.

Exposure

Exposure was defined as BP category at the index date based on the 2017 ACC/AHA BP guideline: normal BP (untreated SBP < 120 mmHg and untreated DBP < 80 mmHg), elevated BP (untreated SBP 120–129 mmHg and untreated DBP < 80 mmHg), stage 1 hypertension (untreated SBP 130–139 mmHg or untreated DBP 80–90 mmHg), and stage 2 hypertension (untreated SBP ≥ 140 mmHg or untreated DBP ≥ 90 mmHg). The Japanese Ministry of Health, Labour and Welfare recommends a specific protocol for obtaining BP measurements in the health checkup system using a standard sphygmomanometer or an automated device [22]. BP was measured on the right arm after participants had rested for 5 min in a seated position. The measurement was performed twice with an interval of ≥ 1 min, and the average value was used.

Outcomes

We defined RVO occurrence as the first date of RVO diagnosis. The ICD-10 code H348 was used to identify any RVO and the more finely-classified Japanese text codes that contain 'central' RVO were used to identify central RVO.

Covariates

We included the following covariates at the index date: sex [13], age [1, 2, 10], obesity [1, 23], diabetes mellitus [13, 24], dyslipidemia [13, 24], smoking status [10, 25], alcohol consumption [18, 26], and glaucoma [13, 27]. These covariates were selected because they have been shown to be associated with occurrence of RVO. Obesity was defined as body mass index ≥ 25 kg/m^2 [2, 28]. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or use of glucose-lowering medications [28]. Dyslipidaemia was defined as low-density lipoprotein-cholesterol ≥ 140 mg/dL, high-density lipoprotein-cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL, or use of lipid-lowering medications [28]. Glaucoma was defined one or more dispensation of any antiglaucoma drug (Anatomical Therapeutic Chemical Classification code S01E, excluding S01EB09) during a 1-year period before the index date.

Statistical analysis

For the complete-case analysis, we excluded individuals with missing data for any covariate. We compared the baseline characteristics between the four BP groups using absolute standardised differences [29]. An absolute standardised difference < 0.1 indicated that the covariates were well-balanced. We estimated the crude cumulative incidence of RVO over 7 years in the entire population using the Kaplan–Meier estimator. This period was chosen because at least 10% of the individuals should remain to avoid a misleading interpretation of cumulative incidence [30]. We estimated crude hazard ratios (HRs) for RVO development using Cox regression in which RVO occurrence was regressed on the BP groups. To further examine the trend, we performed Cox regression in which RVO occurrence was regressed on the BP groups regarded as continuous variables [31]. The assumption of proportional hazards was graphically checked by Schoenfeld residual plots [32]. We replaced the follow-up period of 0 days with 0.5 days ($n = 272$) because the period of 0 days was considered an illegal time interval in the R 'survival' package, which was used in the present study [33].

To minimise potential confounding, we used a matching weight method to balance the baseline characteristics between the groups [34]. The matching weights were based on propensity scores and were shown to be generalizable to multiple treatment groups, demonstrating improved performance over 1:1:1 propensity score matching [34]. To obtain the propensity scores, we constructed multiple binary logistic regression models in which the BP groups were regressed on sex, age, obesity, diabetes mellitus, dyslipidaemia, smoking, alcohol consumption, glaucoma, interaction of age and sex, and interaction of sex and obesity. Using the propensity scores, we calculated matching weights and weighted the BP groups. We checked the balance of the covariates between the weighted groups using standardised differences. We calculated the cumulative incidence of RVO over 7 years for each weighted group using the Kaplan–Meier estimator. We estimated adjusted HRs for RVO compared with the normal BP group using weighted Cox regression. To further examine the trend, we performed Cox regression in which RVO occurrence was regressed on the BP groups regarded as continuous variables. The assumption of proportional hazards was graphically checked by Schoenfeld residual plots. Similar analyses were performed separately for central RVO.

We then calculated the population attributable fraction of each BP group for RVO. Population attributable fraction is a widely used measure to assess the impact of exposures in populations [15]. In the present study, the population attributable fraction represented the RVO case reduction in the population that would occur if stage 1 hypertension was entirely replaced with normal BP. 95% confidence intervals (CIs) were estimated using the Bonferroni inequality method [35]. Similar analyses were performed separately for central RVO.

For the sensitivity analysis, we divided the entire population into two age groups (young [<40 years] and middle-aged [≥ 40 years]).

All analyses were conducted using R software version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with the WeightIt package (version 0.9.0) for calculation of weights. A significance level of 5% was used in all analyses.

RESULTS

A flow chart of the patient selection is shown in Fig. 1. A total of 2,755,335 individuals were eligible. Data were missing for 50,847 (1.8%) individuals for alcohol consumption, 1774 (0.06%) for smoking status, 790 (0.03%) for obesity, 35 (<0.001%) for diabetes mellitus, and 12 (<0.001%) for dyslipidaemia. After removing these individuals with missing data for covariates, we finally included 2,703,262 individuals for the complete-case analysis.

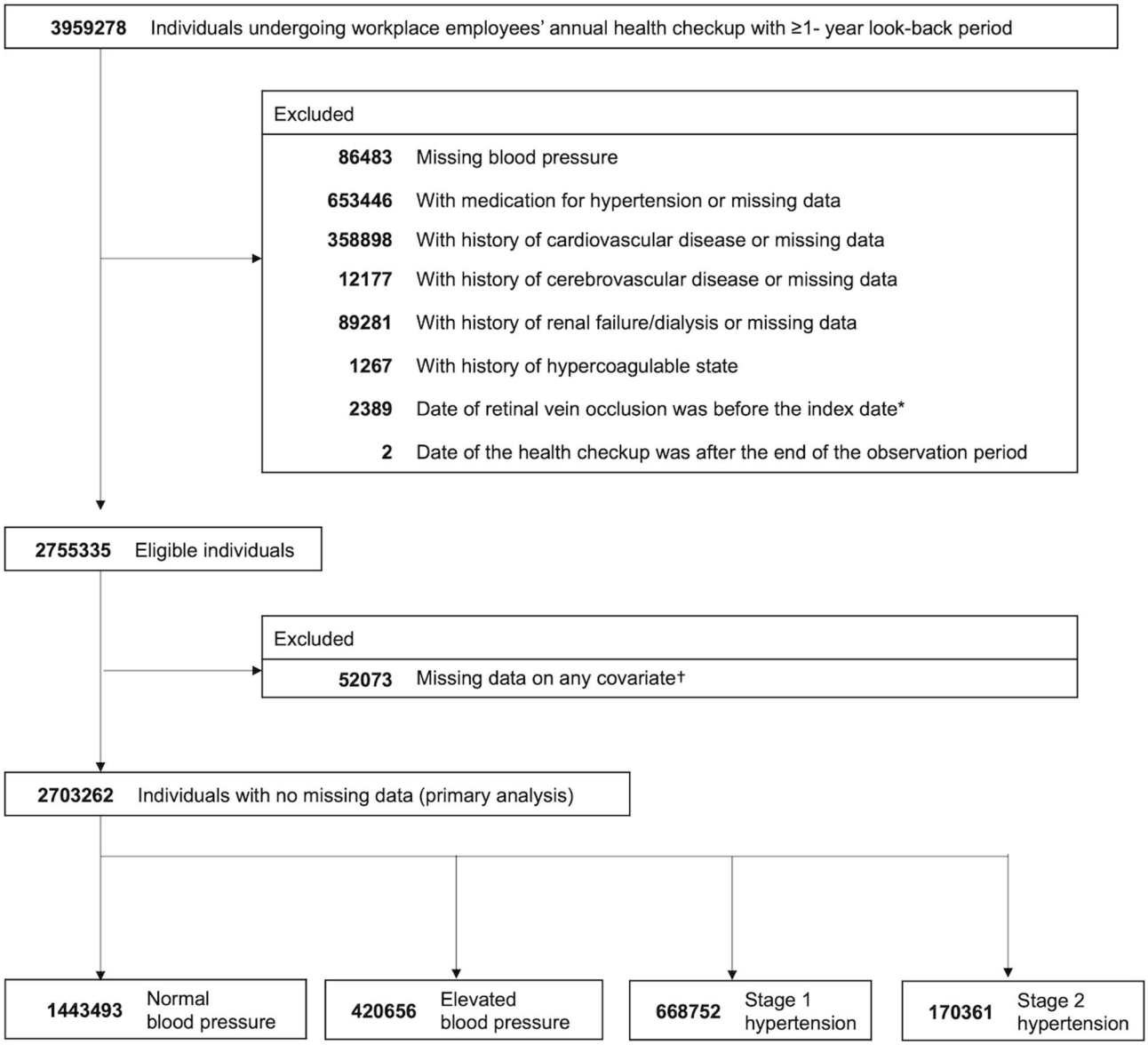

Fig. 1 Patient selection. *The index date was defined as the date of the health checkup. †Missing data was found in 50,847 (1.8%) individuals for alcohol consumption, 1774 (0.06%) for smoking, 790 (0.03%) for obesity, 35 (<0.001%) for diabetes mellitus, and 12 (<0.001%) for dyslipidaemia. Other covariates had no missing data. BP blood pressure.

The patient characteristics before and after weighting by the matching weight method are shown in Table 1. Before weighting, individuals with elevated BP, stage 1 hypertension, and stage 2 hypertension were older and more likely to be male, have obesity, diabetes mellitus, and dyslipidaemia, be a current smoker, drink alcohol frequently, and have glaucoma than individuals with normal BP. After weighting, the absolute standardised differences were <0.1 (Supplementary Fig. 2).

During the mean follow-up of 1,091 days (standard deviation, 925 days; range, 0–4773 days), 3,526 RVO events occurred. The crude cumulative incidence of RVO in the entire population was 0.31% over 7 years. The adjusted cumulative incidence of RVO over 7 years was lowest in the normal BP group (0.31%), followed by the elevated BP group (0.37%), stage 1 hypertension group (0.55%), and stage 2 hypertension group (0.89%) (Fig. 2). The crude HRs for branch RVO occurrence were 1.71 (95% CI, 1.53 to 1.92) for elevated BP, 3.42 (3.14 to 3.71) for stage 1 hypertension, and 6.68 (6.05 to 7.38) for stage 2 hypertension, compared with normal BP (Table 2). The adjusted HRs for branch RVO occurrence were 1.37 (1.19 to 1.57) for elevated BP, 1.95 (1.75 to 2.18) for stage 1 hypertension, and 3.33 (2.95 to 3.76) for stage 2 hypertension, compared with normal BP (Table 2). The P for trend was <0.001. The population attributable fractions for RVO for elevated BP, stage 1 hypertension, and stage 2 hypertension were 3.5% (1.6% to 5.4%), 20.6% (17.0% to 24.2%), and 13.8% (12.0% to 15.8%), respectively.

During the same follow-up period, 828 central RVO events occurred. The crude cumulative incidence of central RVO in the entire population was 0.071% over 7 years. The cumulative incidence of central RVO over 7 years was lowest in the normal BP group (0.065%), followed by the elevated BP group (0.079%), stage 1 hypertension group (0.12%), and stage 2 hypertension group (0.22%) (Fig. 3). The crude HRs for branch RVO occurrence were 1.82 (1.45–2.29) for elevated BP, 3.45 (2.9–4.1) for stage 1 hypertension, and 6.73 (5.47–8.26) for stage 2 hypertension, compared with normal BP (Table 2). The adjusted HRs for branch RVO occurrence were 1.44 (1.07–1.93) for elevated BP, 2.17 (1.72–2.73) for stage 1 hypertension, and 3.76 (2.91–4.86) for stage

Table 1. Baseline characteristics of the patients in the complete-case analysis before and after weighting.

Variable	Unweighted				Weighted			
	Normal BP ($n = 1443493$)	Elevated BP ($n = 420656$)	Stage 1 HTN ($n = 668752$)	Stage 2 HTN ($n = 170361$)	Normal BP ($n = 156258.2$)	Elevated BP ($n = 154758.4$)	Stage 1 HTN ($n = 155564.8$)	Stage 2 HTN ($n = 157696.9$)
Age, mean ± SD	40.9 ± 10.7	42.0 ± 11.9	46.3 ± 10.7	49.2 ± 9.9	48.1 ± 9.9	48.6 ± 10.7	48.1 ± 10.0	48.4 ± 9.7
Male sex	671462 (46.5)	281567 (66.9)	472038 (70.6)	121880 (71.5)	108570.2 (69.5)	108057.9 (69.8)	108968.8 (70.0)	110427.1 (70.0)
Obesity	177897 (12.3)	106571 (25.3)	232011 (34.7)	77596 (45.5)	68409.2 (43.8)	61121.2 (39.5)	64166.0 (41.2)	67522.7 (42.8)
Diabetic mellitus	20317 (1.4)	11715 (2.8)	30646 (4.6)	11955 (7.0)	9012.8 (5.8)	8664.8 (5.6)	8647.0 (5.6)	9411.2 (6.0)
Dyslipidaemia	399654 (27.7)	161182 (38.3)	327385 (49.0)	96553 (56.7)	86616.7 (55.4)	82499.7 (53.3)	83888.0 (53.9)	86833.9 (55.1)
Current smoker	339150 (23.5)	119862 (28.5)	195420 (29.2)	51538 (30.3)	47957.0 (30.7)	46562.5 (30.1)	46991.9 (30.2)	47613.0 (30.2)
Alcohol drinking								
Daily	228369 (15.8)	86807 (20.6)	194629 (29.1)	58580 (34.4)	49311.5 (31.6)	48127.9 (31.1)	48948.1 (31.5)	50553.9 (32.1)
Sometimes	556367 (38.5)	156500 (37.2)	232589 (34.8)	54412 (31.9)	51461.7 (32.9)	51470.2 (33.3)	51913.1 (33.4)	51936.4 (32.9)
Rarely	658757 (45.6)	177349 (42.2)	241534 (36.1)	57369 (33.7)	55485.0 (35.5)	55160.3 (35.6)	54703.6 (35.2)	55206.6 (35.0)
Glaucoma	20739 (1.4)	6098 (1.4)	12626 (1.9)	3518 (2.1)	3170.6 (2.0)	3146.2 (2.0)	3012.3 (1.9)	3170.9 (2.0)

BP Blood pressure.
Data are presented as n (%) unless otherwise indicated.
Individuals were categorized into normal BP (untreated systolic blood pressure [SBP] < 120 mmHg and diastolic blood pressure [DBP] < 80 mmHg), elevated BP (untreated SBP 120–129 mmHg and DBP < 80 mmHg), stage 1 hypertension (untreated SBP 130–139 mmHg or DBP 80–89 mmHg), and stage 2 hypertension (untreated SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) groups.

Fig. 2 Cumulative incidence curves of any retinal vein occlusion weighted by matching weights. Normal normal blood pressure (untreated systolic blood pressure [SBP] < 120 mmHg and diastolic blood pressure [DBP] < 80 mmHg); elevated = elevated blood pressure (untreated SBP 120–129 mmHg and DBP < 80 mmHg); stage 1 = stage 1 hypertension (untreated SBP 130–139 mmHg or DBP 80–89 mmHg); stage 2 = stage 2 hypertension (untreated SBP ≥ 140 mmHg or DBP ≥ 90 mmHg).

2 hypertension, compared with normal BP (Table 2). The P for trend was <0.001. The population attributable fractions for central RVO for elevated BP, stage 1 hypertension, and stage 2 hypertension were 4.1% (0.3–8.3%), 22.6% (15.3–29.7%), and 14.5% (10.8–18.5%), respectively.

Sensitivity analyses

In the sensitivity analysis, individuals aged <40 and ≥40 years showed similar HRs to the primary analysis (Supplementary Table 1 and Supplementary Table 2). The incidences in individuals aged < 40 years were low and some HRs did not reach statistical significance.

DISCUSSION

The present study using data from a large claims database showed that elevated BP, stage 1 hypertension, and stage 2 hypertension were significantly associated with higher risks for development of RVO and central RVO compared with normal BP. The risks increased stepwise according to the BP groups. Furthermore, the significant positive values of the population attributable fractions for RVO and central RVO indicated that RVO and central RVO could be attributed to stage 1 hypertension and stage 2 hypertension.

Lowering the threshold for hypertension by 10 mmHg was a major revision with great meaning for medicine and public health. Clinical evidence supporting the validity of the 2017 ACC/AHA guideline has accumulated in recent years, especially in the field of cardiology [28, 36–39]. The present findings showed that individuals with elevated BP and stage 1 hypertension had higher risks of developing RVO than individuals with normal BP, thereby reinforcing the validity of the guideline from the view of ophthalmology.

The cumulative incidences of any RVO were reported to be 3.0% over 9 years in Japan [11], 1.9% over 10 years in China [12], and 1.6% over 10 years in Australia [1]. Compared with these studies, the present study showed lower incidences. This probably arose because the individuals in the present study were younger (mean age after weighting, 48 years) than the individuals in the previous studies (mean age: Japanese study, 60 years; [11] Chinese study, 55 years [12]; Australian study, ≥52 years [1]). Young individuals are generally less likely to develop RVO. In fact, our first sensitivity analysis showed that individuals aged <40 years had fewer RVO events than individuals aged ≥ 40 years. Another explanation for the lower incidences in the present study may be related to

Table 2. Hazard ratios and population attributable fractions for any retinal vein occlusion and central retinal vein occlusion before and after weighting.

	Unweighted[a]			Weighted[b]			
BP group	***N***	**No. of events (%)**	**HR (95% CI)**	***N***	**No. of events (%)**	**HR (95% CI)**	**Population attributable fraction, % (95% CI)**
(A) Any retinal vein occlusion							
Normal BP	1443493	885 (0.06)	1 (ref)	156258.2	192.0 (0.12)	1 (ref)	0 (ref)
Elevated BP	420656	455 (0.11)	1.71 (1.53–1.92)	154758.4	260.7 (0.17)	1.37 (1.19–1.57)	3.5 (1.6–5.4)
Stage 1 hypertension	668752	1489 (0.22)	3.42 (3.14–3.71)	155564.8	381.9 (0.25)	1.95 (1.75–2.18)	20.6 (17.0–24.2)
Stage 2 hypertension	170361	697 (0.41)	6.68 (6.05–7.38)	157696.9	627.8 (0.4)	3.33 (2.95–3.76)	13.8 (12.0–15.8)
P for trend			<0.001			<0.001	
(B) Central retinal vein occlusion							
Normal BP	1443493	205 (0.01)	1 (ref)	156258.2	39.9 (0.03)	1 (ref)	0 (ref)
Elevated BP	420656	112 (0.03)	1.82 (1.45–2.29)	154758.4	57.1 (0.04)	1.44 (1.07–1.93)	4.1 (0.3–8.3)
Stage 1 hypertension	668752	348 (0.05)	3.45 (2.9–4.1)	155564.8	88.3 (0.06)	2.17 (1.72–2.73)	22.6 (15.3–29.7)
Stage 2 hypertension	170361	163 (0.1)	6.73 (5.47–8.26)	157696.9	147.7 (0.09)	3.76 (2.91–4.86)	14.5 (10.8–18.5)
P for trend			<0.001			<0.001	

BP Blood pressure, *HR* Hazard ratio, *CI* Confidence interval, *ref.* Reference. [a]HRs in the unweighted groups represent crude HRs.
[b]HRs in the weighted groups represent adjusted HRs.

Fig. 3 Cumulative incidence curves of central retinal vein occlusion weighted by matching weights. normal = normal blood pressure (untreated systolic blood pressure [SBP] < 120 mmHg and diastolic blood pressure [DBP] < 80 mmHg); elevated = elevated blood pressure (untreated SBP 120–129 mmHg and DBP < 80 mmHg); stage 1 = stage 1 hypertension (untreated SBP 130–139 mmHg or DBP 80–89 mmHg); stage 2 = stage 2 hypertension (untreated SBP ≥ 140 mmHg or DBP ≥ 90 mmHg).

differences between the above-reference studies [1, 11, 12] and the present study in terms of data collection. The above studies were population-based complete surveys, which included both individuals with symptomatic RVO and individuals with asymptomatic RVO. In contrast, the present study was based on claims data, which only included data from symptomatic patients with RVO because individuals with asymptomatic RVO do not present to hospitals for treatment; accordingly, they cannot be diagnosed with RVO. Thus, the incidence of RVO may have been lower in the present study than in the previous studies.

Previous studies investigated the association between hypertension severity and RVO occurrence [13, 24]. They found that individuals with uncomplicated hypertension (no end-organ damage) had higher risks for branch RVO and central RVO compared with normotensive individuals, while individuals with complicated hypertension (presence of end-organ damage) had even higher risks. However, the classification of hypertension in these studies was based on ICD-9 codes rather than actual BP measurements. Although a Japanese population-based study used actual BP values to investigate the risk factors for RVO, the number of RVO occurrences was [40] and thus too small to draw any inference [11]. Furthermore, these previous studies did not use the threshold defined by the ACC/AHA guideline. We classified the individuals into normal BP, elevated BP, stage 1 hypertension, and stage 2 hypertension groups using actual BP measurements and the ACC/AHA guideline. Consequently, we obtained the new insight that early-stage hypertension states such as elevated BP and stage 1 hypertension were associated with RVO among young and middle-aged adults.

The present results suggest that elevated BP should be considered with caution from an early stage, which was not regarded as a treatment target before the publication of the 2017 ACC/AHA guideline [14]. Doctors should encourage patients to make healthy choices with regard to their diet and physical activity as recommended by the guideline. Efforts to change lifestyle factors can reduce the risk for cardiovascular diseases as previously described [39]. Such efforts would also decrease the risk for RVO, leading to preservation of visual acuity and improved quality of life. Fewer RVO events will reduce the physical, psychological, and financial burden on patients. Moreover, healthcare costs would be saved because of the reduced need to use expensive intravitreal anti-vascular endothelial growth factor drugs for treatment of macular oedema caused by RVO.

The population attributable fractions for RVO were highest in the stage 1 hypertension group. These results indicate that the stage 1 hypertension group would have the most influence on the population if BP was made normal in all individuals. For example, 20.6% of RVO occurrences would be prevented if these individuals did not have stage 1 hypertension (i.e. had normal BP). Thus, we need to pay attention to not only stage 2 hypertension but also stage 1 hypertension to prevent RVO occurrence. However, population attributable fractions assume that there is a perfect intervention to eradicate the exposure [15]. This assumption is often unrealistic. Thus, in future studies, we need to investigate the extent of the effect that decreasing BP has on individuals with early-stage hypertension using real-world data.

One of the strengths of the present study is that we were able to obtain specific numerical data on BP. Furthermore, we were able to follow individuals in a very large sample size longitudinally over a long period of time. Given the relatively low incidence of RVO, performance of randomised controlled studies would be difficult. Thus, the findings obtained in this observational study are useful for filling the evidence gap.

There are several limitations to the present study. First, because almost all of the individuals in the database were working-age Asians, the results may not be generalizable to other races, ethnicities, and education levels. However, given that a meta-analysis did not show associations between races and prevalence of RVO [2], racial differences may not be very important. Second, BP was measured in individuals on a single occasion during a health checkup. Therefore, this BP may not fully reflect the BP phenotype of the individuals. For example, BP measured during health checkups may have been higher than that measured at home. A case-control study reported an association between RVO and BP variability [41], and thus further studies with measurement of 24-hour ambulatory BP are warranted. Third, the protocol for BP measurement, established by the Japanese Ministry of Health, Labour and Welfare, may not have been completely followed in real-world settings. Fourth, the prevalence of RVO was lower in the present study than in previous population-based complete surveys [1, 11, 12]. This difference is presumably because the present study, which used claims data, could not include individuals with asymptomatic RVO, while the complete surveys could include such individuals. However, comparisons of different BP groups in a limited population with symptomatic RVO would be valid. Fifth, the codes of claims data are not entirely accurate. A validation study in Japan showed that the diagnosis of age-related macular degeneration in claims data had a high sensitivity (94.9%) and a high specificity (92.6%) [40]; however, such validation studies have not been performed with regard to RVO. In some RVO cases, the RVO diagnostic codes may not have been registered because the patients did not require treatment; this phenomenon may have contributed to underestimation of the incidence. However, we believe that the specificity of the RVO codes was relatively high; comparisons of different BP groups in a limited population with RVO codes would be valid.

In conclusion, occurrence of RVO and central RVO was found to be associated with elevated BP and stage 1 hypertension. The BP categorization advocated by the 2017 ACC/AHA guideline can be useful for identifying young and middle-aged adults at increased risk for RVO.

SUMMARY

What was known before

- One of the major and modifiable risk factors for retinal vein occlusion is hypertension.
- The threshold of hypertension was lowered to 130/80 mmHg by the 2017 American College of Cardiology/American Heart Association blood pressure guideline, but the association between early-stage hypertension and retinal vein occlusion is unknown.

What this study adds

- Using a large administrative claims database, we found that even early-stage hypertension was associated with the occurrence of retinal vein occlusion.

DATA AVAILABILITY

We used de-identified, individual-level data obtained from the JMDC Claims Database (Tokyo, Japan). The address of their HP is https://www.jmdc.co.jp/en/index. Data are not publicly available.

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AUTHOR CONTRIBUTIONS

YH had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YH, HK, AO, HY, and RO. Acquisition, analysis, and interpretation of data: YH, HK, SA, AO, HM, HY, RO. Drafting of the manuscript: YH, HK, HY, and AO. Critical revision of the manuscript for important intellectual content: YH. Statistical analysis: YH, SA, AO, and HY. Obtained funding: HY. Administrative, technical, or material support: None. Study supervision: HY and AO.

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COMPETING INTERESTS

The authors declare no competing interests.

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