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Hypertension as a risk factor for retinal vein occlusion in menopausal women

A nationwide Korean population-based study

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Abstract

Retinal vein occlusion (RVO) is an important cause of blindness. Hypertension is a well-known risk factor for RVO. Although the prevalence of hypertension increases in women after menopause, the relationship between blood pressure and RVO in women before and after menopause has not been studied in detail.

We retrospectively analyzed 2,619,206 patients from the Korean National Health Insurance System database. A Cox proportional hazard regression model was used to evaluate the independent association between blood pressure and the risk of RVO development and identify differences between premenopausal and postmenopausal women.

The incidence of RVO was higher among postmenopausal women than in premenopausal women. In the model adjusted for socioeconomic and clinical variables, there was an association between blood pressure and RVO development in premenopausal and postmenopausal women; however, this was stronger than premenopausal women.

Both systolic and diastolic blood pressure are associated with an increased risk of RVO, and their effects are more potent in premenopausal women than postmenopausal women. Thus, comprehensive management of hypertension in premenopausal women is essential to reduce the risk of RVO.

Abbreviations: CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, ICD = International Classification of Diseases, IR = incidence rate, RVO = retinal vein occlusion.

Keywords: blood pressure, hypertension, post-menopause, pre-menopause, retinal vein occlusion

1. Introduction

Among retinal vascular disease, retinal vein occlusion (RVO) is the second leading cause of loss of vision after diabetic retinopathy.[1,2] RVO is classified into central RVO and branch RVO. In central RVO, the central retinal vein is occluded as it exits the optic nerve. In branch RVO, vascular occlusion occurs in the branches of the retinal vein system.[3,4] The pathophysiology of RVO is multifactorial and not completely understood. However, the pathogeneses of central RVO and branch RVO are reported to be significantly different.[5] Branch RVO primarily occurs due to the compression of the branches of the central retinal vein at the arteriovenous crossing,[2] whereas central RVO is primarily caused by thrombosis and occlusion of the central retinal vein within the optic nerve.[3] The prevalence of RVO has been reported to be about 0.7% to 1.6%,[5,6] and branch RVO is 6 times more prevalent than central RVO.[7] The incidence of RVO is approximately 2.3% to 3%, and a higher incidence of branch RVO than of central RVO was reported in a Japanese study[8] and in the Beaver Dam Eye Study.[1]

RVO occurs mainly in the elderly,[9] and additional risk factors include smoking[1] and systemic diseases, such as hypertension,[5,10,11] diabetes mellitus (DM),[1] dyslipidemia,[5,10] and a past history of angina.[5] Moreover, RVO was reported to be associated with cardiovascular disease,[12,13] and the risk factors for RVO are closely related to those of cardiovascular disease.[14] In particular, hypertension is a major risk factor for RVO, and the importance of blood pressure control has also been emphasized. Women experience significant physiologic changes

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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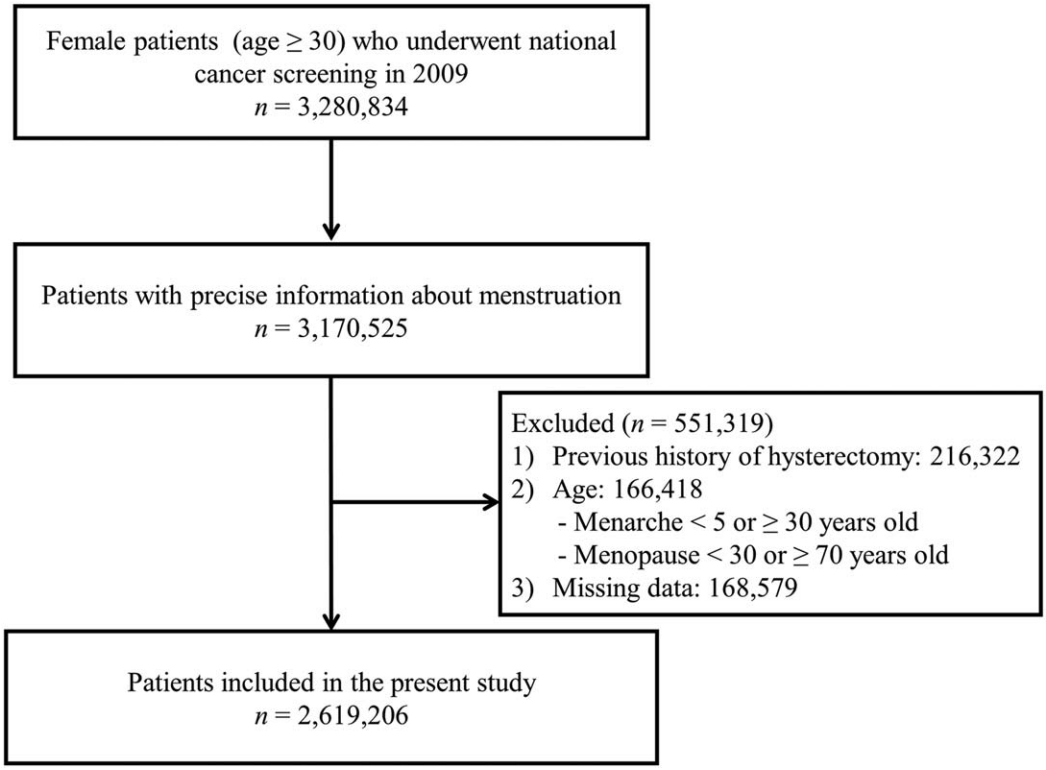

Figure 1. Flow diagram showing the study design.

during menopause, including increased blood pressure that results in an increased prevalence of hypertension compared to premenopausal women.[15,16] These changes may differentially influence the relationship of blood pressure with RVO in premenopausal women compared to postmenopausal women; however, this has not been investigated thoroughly. In addition, only a few population-based studies of RVO have been performed in Asians.[5,8,17,18] This study aimed to identify the association between blood pressure and RVO development using a large population and analyze the differences in the effect of hypertension on the risk of RVO between premenopausal women and postmenopausal women.

2. Materials and methods

2.1. Data source and study population

This was a retrospective observational study. We analyzed the Korean National Health Insurance System database, which covers almost all (approximately 97%) Korean citizens.[19] The database includes demographic information, medical bills claimed by medical services, health examination findings, and medical care institutions. The National Health Insurance Corporation's subscribers are advised to undergo standard medical examinations at least every 2 years.

Among 3,280,834 patients who underwent national cancer screening in 2009, 110,309 cases with incomplete information regarding menstruation history were excluded. Furthermore, 382,740 subjects who did not meet the age requirement or who had missing data and 216,322 subjects with a history of hysterectomy were excluded. A total of 2,619,206 patients were analyzed and followed up until 2018. Figure 1 shows the patient selection flowchart.

2.2. Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Chonnam National University Hospital Institutional Review Board (CNUHEXP-2020–182). The database used in this study did not include personal identifiers, and the study was retrospective and observational in nature; therefore, the requirement for informed consent was waived.

2.3. Endpoint and definitions

The primary endpoint of this study was newly diagnosed RVO, which was defined using a combination of International Classification of Disease, 10th Revision (ICD-10) code H348. We used standardized self-reported questionnaires to collect data for age (years), alcohol consumption (none; mild, <30 g of alcohol/day; heavy ≥30 g of alcohol/d), smoking status (never, former, and current), menopause history, and use of hormone replacement therapy. Regular physical exercise was defined as regular strenuous exercise (high-intensity activity ≥3 times/wk; moderate-intensity activity,≥5 times/wk; none).[20] DM was defined based on the presence of fasting glucose level ≥126 mg/dL (from health examination data) or at least one prescription of antidiabetic medication per year with ICD-10 codes E11–14. Hypertension was defined as the presence of at least one claim per year of antihypertensive medication or systolic/diastolic blood pressure of 140/90 mm Hg with ICD-10 codes I10–15.[21] The

use of antihypertensive and antidiabetic medications was defined as the presence of a prescription for an antihypertensive medication within 6 months from the date of medical examination. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Abdominal obesity was defined as waist circumference ≥90 cm for men and ≥85 cm for women.[22] The body mass index was calculated by dividing the body weight (kilogram) by the square of the height in meters. Dyslipidemia was defined as a total cholesterol level >240 mg/dL or prescription of an antihyperlipidemic medication with ICD-10 codes E78. Low income was defined as cases where the sum of medical aid and income was in the bottom 20%. Patients in both the pre- and postmenopausal women groups were divided into 8 categories of systolic blood pressure: <100, 100–110, 110–120, 120–130, 130–140, 140–150, 150–160, and ≥160 mm Hg.

2.4. Statistical analyses

Continuous variables with normal distribution were expressed as mean (± standard deviation). Student *t*-test was used to compare continuous variables between the 2 groups. Skewed data were described as median with interquartile range, and the Mann-Whitney *U* test was used for skewed data to identify differences and compare clinical characteristics between groups. Categorical variables were described as the number of participants (percentage) and were compared using the chi-squared test. Incidence rates were calculated by dividing the number of events by the person-time at risk. A Cox proportional hazard regression model was applied to analyze the independent association between blood pressure and the risk of RVO development, and the hazards ratio (HR) and 95% confidence interval were calculated. We verified the PH assumption using Schoenfeld residual plot and log-log survival function plot. The model was adjusted for age, sex, smoking status, alcohol consumption, body mass index, regular physical exercise, low income, DM, dyslipidemia, CKD, use of antihypertensive medication, and hormone replacement therapy in the final Cox proportional hazard model. However, hormone replacement therapy was excluded from the analyses when calculating the *P* values of interaction in Cox proportional hazard models; hence, the independent variables used in each Cox proportional hazard model are described as annotations in the figures and tables. All statistical tests were two-tailed, and $P < .05$ was considered statistically significant. SAS version 9.3 software and SAS survey procedures (SAS Institute, Inc., Cary, NC) were used for all statistical analyses.

3. Results

3.1. Clinical characteristics of the participants

Of the 2,619,206 patients included, 1,454,048 (55.51%) were postmenopausal women. The baseline characteristics of the pre- and postmenopausal women groups are summarized in Table 1. The mean ages of participants in the pre- and postmenopausal women groups were 43.8 years and 61.8 years, respectively. The

Table 1

Clinical characteristics for study population.

Variables	Pre-menopausal women (*n*=1,165,158)	Post-menopausal women (*n*=1,454,048)	*P*-value
Age (yr)	43.84±5.41	61.86±8.51	< .001
SBP (mm Hg)	116.64±14.23	125.79±16.23	< .001
DBP (mm Hg)	72.8±9.91	76.97±10.18	< .001
Height (cm)	157.79±5.24	153.4±5.75	< .001
Weight (kg)	57.44±8.18	56.97±8.32	< .001
BMI (kg/m^2)	23.07±3.11	24.19±3.16	< .001
WC (cm)	74.9±8.18	80.12±8.6	< .001
Glucose (mg/dl)	93.27±17.57	99.84±24.51	< .001
TC (mg/dl)	190.72±39.05	208±44.36	< .001
Anti-HTN medication	104507 (8.97)	572078 (39.34)	< .001
DM (%)	39119 (3.36)	193536 (13.31)	< .001
CKD (%)	48437 (4.16)	177293 (12.19)	< .001
Dyslipidemia (%)	124401 (10.68)	496151 (34.12)	< .001
Obesity (%)	274113 (23.53)	543735 (37.39)	< .001
Abdominal obesity (%)	132097 (11.34)	412764 (28.39)	< .001
Regular Exercise (%)	191484 (16.43)	264646 (18.2)	< .001
Smoking (%)			< .001
Non	1100451 (94.45)	1399066 (96.22)	
Ex	22326 (1.92)	15599 (1.07)	
Current	42381 (3.64)	39383 (2.71)	
Drinking (%)			< .001
Non	819724 (70.35)	1276022 (87.76)	
Mild	331642 (28.46)	170688 (11.74)	
Heavy	13792 (1.18)	7338 (0.5)	
Income * (%)	259437 (22.27)	276236 (19)	< .001
HRT (%)	-	231754 (15.94)	< .001
RVO (%)	6932 (0.59)	30558 (2.1)	< .001
RVO duration (years)	9.29 (9.09–9.54)	9.42 (9.12–9.7)	< .001

BMI = body mass index, CKD = chronic kidney disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HRT = hormone replacement therapy, HTN = hypertension; RVO = retinal vein occlusion, SBP = systolic blood pressure, TC = total cholesterol, WC = waist circumference.

* low income 25%.

Table 2

Clinical characteristics of participants by categories of systolic blood pressure in pre-menopausal women.

	Distribution of systolic blood pressure (mm Hg)								
Variables	**< 100 (n = 83876)**	**100-110 (n = 234236)**	**110-120 (n = 351566)**	**120-130 (n = 262925)**	**130-140 (n = 163866)**	**140-150 (n = 38685)**	**150-160 (n = 18281)**	**≥ 160 (n = 11723)**	***P*-value**
Age (yr)	42.34 ± 5.25	42.68 ± 5.23	43.4 ± 5.25	44.21 ± 5.3	45.39 ± 5.29	46.47 ± 5.45	46.89 ± 5.57	47.02 ± 5.74	< .001
SBP (mm Hg)	93.23 ± 4.1	103.24 ± 3.23	113 ± 3.27	122.42 ± 3	132.67 ± 3.11	142.3 ± 2.91	151.9 ± 2.77	167.84 ± 10.71	< .001
DBP (mm Hg)	60.16 ± 5.21	64.85 ± 5.84	70.71 ± 5.84	76.55 ± 6.2	81.3 ± 6.47	88.1 ± 7.64	92.81 ± 8.24	99.91 ± 11.02	< .001
Height (cm)	157.98 ± 5.19	158.12 ± 5.19	157.98 ± 5.23	157.74 ± 5.24	157.33 ± 5.25	156.86 ± 5.28	156.71 ± 5.28	156.37 ± 5.33	< .001
Weight (cm)	53.86 ± 6.49	55.32 ± 6.94	56.92 ± 7.61	58.35 ± 8.27	60.08 ± 8.96	61.63 ± 9.62	62.3 ± 9.93	62.77 ± 10.4	< .001
BMI (kg/m2)	21.58 ± 2.42	22.12 ± 2.59	22.81 ± 2.87	23.45 ± 3.11	24.26 ± 3.36	25.03 ± 3.6	25.35 ± 3.71	25.64 ± 3.89	< .001
WC (cm)	71.5 ± 6.54	72.75 ± 7.12	74.27 ± 7.67	75.76 ± 8.09	77.61 ± 9.17	79.36 ± 8.82	80.07 ± 8.93	80.78 ± 9.39	< .001
Glucose (mg/dl)	89.33 ± 12.82	90.57 ± 14.03	92.38 ± 16	94.22 ± 18.11	96.7 ± 21.13	99 ± 23.51	100.61 ± 25.01	102.01 ± 27.51	< .001
TC (mg/dl)	182.69 ± 33.56	185.56 ± 36.63	189.13 ± 37.8	193.03 ± 40.68	197.22 ± 40.61	200.65 ± 43.91	202.35 ± 45.26	205.18 ± 39.91	< .001
Anti-HTN medication (%)	2927 (3.49)	9339 (3.99)	20921 (5.95)	25340 (9.64)	27317 (16.67)	10111 (26.14)	5268 (28.82)	3284 (28.01)	< .001
DM (%)	1006 (1.2)	3858 (1.65)	8837 (2.51)	9945 (3.78)	9427 (5.75)	3078 (7.96)	1714 (9.38)	1254 (10.7)	< .001
CKD (%)	3149 (3.75)	8729 (3.73)	14152 (4.03)	11267 (4.29)	7520 (4.59)	2004 (5.18)	918 (5.02)	698 (5.95)	< .001
Dyslipidemia (%)	4738 (5.65)	16443 (7.02)	31754 (9.03)	31397 (11.94)	25730 (15.7)	7668 (19.82)	3915 (21.42)	2756 (23.51)	< .001
Obesity (%)	7135 (8.51)	30715 (13.11)	70939 (20.18)	72187 (27.46)	60472 (36.9)	17588 (45.46)	9007 (49.27)	6070 (51.78)	< .001
Abdominal obesity (%)	2938 (3.5)	12852 (5.49)	31709 (9.02)	34698 (13.2)	31209 (19.05)	9903 (25.6)	5160 (28.23)	3628 (30.95)	< .001
Regular Exercise (%)	12800 (15.26)	37001 (15.8)	57680 (16.41)	44027 (16.75)	28216 (17.22)	6739 (17.42)	3073 (16.81)	1948 (16.62)	< .001
Smoking (%)									< .001
Non	77185 (92.02)	219037 (93.51)	332648 (94.62)	249751 (94.99)	156347 (95.41)	36867 (95.3)	17487 (95.66)	11129 (94.93)	
Ex	2329 (2.78)	5484 (2.34)	6783 (1.93)	4452 (1.69)	2378 (1.45)	534 (1.38)	216 (1.18)	150 (1.28)	
Current	4362 (5.2)	9715 (4.15)	12135 (3.45)	8722 (3.32)	5141 (3.14)	1284 (3.32)	578 (3.16)	444 (3.79)	
Drinking (%)									< .001
Non	59783 (71.28)	165024 (70.45)	247902 (70.51)	183788 (69.9)	114982 (70.17)	27073 (69.98)	13014 (71.19)	8158 (69.59)	
Mild	23383 (27.88)	67118 (28.65)	99794 (28.39)	75755 (28.81)	46514 (28.39)	10875 (28.11)	4931 (26.97)	3272 (27.91)	
Heavy	710 (0.85)	2094 (0.89)	3870 (1.1)	3382 (1.29)	2370 (1.45)	737 (1.91)	336 (1.84)	293 (2.5)	
Low income* (%)	16787 (20.01)	49637 (21.19)	78377 (22.29)	60215 (22.9)	38487 (23.49)	8894 (22.99)	4317 (23.61)	2723 (23.23)	< .001
RVO (%)	281 (0.34)	903 (0.39)	1800 (0.51)	1677 (0.64)	1426 (0.87)	439 (1.13)	217 (1.19)	189 (1.61)	< .001
RVO duration (yr)	9.33 (9.12;9.54)	9.31 (9.1;9.54)	9.3 (9.1;9.54)	9.28 (9.08;9.54)	9.27 (9.08;9.55)	9.29 (9.08;9.56)	9.28 (9.07;9.56)	9.24 (9.06;9.56)	< .001

BMI = body mass index, CKD, chronic kidney disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HTN = hypertension, RVO = retinal vein occlusion, SBP = systolic blood pressure, TC = total cholesterol, WC = waist circumference.

* Low income 25%.

prevalence of DM, CKD, and abdominal obesity was higher in the premenopausal women group than in the postmenopausal women group. The mean systolic blood pressure was higher in the postmenopausal women group than in the premenopausal women group (125.79 ± 16.23 and 116.64 ± 14.23 mm Hg, respectively). The use of antihypertensive treatment in the postmenopausal women group (39.34%) was higher than in the premenopausal women group (8.97%). A total of 231,754 patients in the postmenopausal women group received hormone replacement therapy. Of the 1,165,158 premenopausal patients, 6,932 (0.59%) were newly diagnosed with RVO. Meanwhile, out of 1,454,048 subjects in the postmenopausal women group, 30,558 patients were diagnosed with RVO. The mean follow-up periods of the two groups were 9.29 (9.09; 9.54) years in the premenopausal women group and 9.42 (9.12; 9.7) years in the postmenopausal women group. The characteristics of patients in the 8 categories of systolic blood pressure are summarized in Table 2 (premenopausal women) and Table 3 (postmenopausal women). Regardless of menopause, we observed an increase in the prevalence of diabetes, dyslipidemia, and obesity as with an increase in blood pressure.

3.2. Association between systolic blood pressure and retinal vein occlusion development

The incidence rate (IR) of RVO was higher in the postmenopausal women group than in the premenopausal women group. The IR of RVO increased steadily with every incremental change in systolic blood pressure in both groups (Table 4). Systolic blood pressure was associated with the risk of RVO in both the pre- and postmenopausal women groups in the fully adjusted Cox proportional hazard model (Fig. 2); however, there was a statistically significant difference between the two groups (*P* for interaction < .001). In the premenopausal women group, an elevation of systolic blood pressure steadily increased the HR of RVO. In the postmenopausal women group, the HR of RVO increased as systolic blood pressure increased from <100 mm Hg to 120 to 130 mm Hg; however, no significant change in HR was observed with an increase in systolic blood pressure from 130 mm Hg to ≥160 mm Hg.

3.3. Association between diastolic blood pressure and retinal vein occlusion development

The IR of RVO was higher in the postmenopausal women group than in the premenopausal women group in each category of diastolic blood pressure. The IR of RVO increased steadily with an elevation of diastolic blood pressure in both groups (Table 5). As with systolic blood pressure, diastolic blood pressure was associated with RVO in the fully adjusted Cox proportional hazard model (Fig. 3). There was a statistically significant difference in the risk of RVO between the two groups (*P* for interaction < .001). In the premenopausal women group, patients with a diastolic blood pressure of <70 mm Hg showed a lowest risk of RVO and those with a diastolic blood pressure of ≥100 mm Hg showed a highest risk of RVO. In the postmenopausal

Table 3

Clinical characteristics of participants by categories of systolic blood pressure in post-menopausal women.

	Distribution of systolic blood pressure (mm Hg)								
Variables	< 100 (n = 39127)	100-110 (n = 129428)	110-120 (n = 309847)	120-130 (n = 335960)	130-140 (n = 374434)	140-150 (n = 132652)	150-160 (n = 76173)	≥ 160 (n = 56427)	*P*-value
Age (yr)	57.22 ± 7.36	58.18 ± 7.61	60.28 ± 8.18	61.35 ± 8.27	63.19 ± 8.4	64.25 ± 8.35	65.04 ± 8.37	66.35 ± 8.54	< .001
SBP (mm Hg)	93.02 ± 4.23	103.19 ± 3.28	113.34 ± 3.49	122.59 ± 3.13	132.86 ± 3.33	142.13 ± 2.89	151.73 ± 2.72	167.37 ± 9.8	< .001
DBP (mm Hg)	60.32 ± 5.37	65.12 ± 6.05	71.04 ± 5.93	76.19 ± 6.4	80.34 ± 6.66	85.18 ± 7.99	89.1 ± 8.71	94.85 ± 10.85	< .001
Height (cm)	154.56 ± 5.54	154.45 ± 5.58	153.9 ± 5.69	153.63 ± 5.69	153.02 ± 5.74	152.7 ± 5.75	152.31 ± 5.78	151.68 ± 5.87	< .001
Weight (cm)	53.51 ± 7.11	54.96 ± 7.4	56.15 ± 7.88	57.1 ± 8.13	57.73 ± 8.51	58.31 ± 8.79	58.22 ± 8.98	57.84 ± 9.34	< .001
BMI	22.39 ± 2.7	23.02 ± 2.8	23.68 ± 2.96	24.17 ± 3.06	24.62 ± 3.18	24.97 ± 3.28	25.05 ± 3.34	25.09 ± 3.48	< .001
WC (cm)	75.09 ± 7.5	76.74 ± 8.23	78.58 ± 8.07	80.01 ± 8.14	81.38 ± 8.57	82.43 ± 8.75	82.78 ± 8.99	83.15 ± 9.11	< .001
Glucose (mg/dl)	94.01 ± 19.86	95.35 ± 20.69	97.84 ± 22.55	99.38 ± 23.73	101.28 ± 25.41	103.09 ± 26.99	103.86 ± 27.36	105.23 ± 29.72	< .001
TC (mg/dl)	202.27 ± 38.25	204.79 ± 41.78	206.41 ± 42.87	207.88 ± 44.22	209.14 ± 45.32	209.95 ± 47.88	210.94 ± 45.54	212.77 ± 45.08	< .001
Anti-HTN medication (%)	5656 (14.46)	24565 (18.98)	87225 (28.15)	124538 (37.07)	178044 (47.55)	74494 (56.16)	44246 (58.09)	33310 (59.03)	<.001
DM (%)	2415 (6.17)	9940 (7.68)	32306 (10.43)	42725 (12.72)	57035 (15.23)	23313 (17.57)	14169 (18.6)	11633 (20.62)	<.001
CKD (%)	3399 (8.69)	11698 (9.04)	32919 (10.62)	38902 (11.58)	49803 (13.3)	19450 (14.66)	11496 (15.09)	9626 (17.06)	<.001
Dyslipidemia (%)	9297 (23.76)	35006 (27.05)	93922 (30.31)	114831 (34.18)	137297 (36.67)	52369 (39.48)	30556 (40.11)	22873 (40.54)	<.001
Obesity (%)	6170 (15.77)	29032 (22.43)	95308 (30.76)	124110 (36.94)	161317 (43.08)	62986 (47.48)	37031 (48.61)	27781 (49.23)	<.001
Abdominal obesity (%)	4169 (10.66)	19553 (15.11)	67265 (21.71)	91904 (27.36)	124859 (33.35)	50961 (38.42)	30510 (40.05)	23543 (41.72)	<.001
Regular Exercise (%)	7570 (19.35)	25281 (19.53)	58955 (19.03)	62679 (18.66)	66192 (17.68)	23339 (17.59)	12336 (16.19)	8294 (14.7)	<.001
HRT (%)	9184 (23.47)	27895 (21.55)	55243 (17.83)	57271 (17.05)	52414 (14)	16978 (12.8)	8096 (10.63)	4673 (8.28)	<.001
Smoking (%)									<.001
Non	36466 (93.2)	122490 (94.64)	297045 (95.87)	323488 (96.29)	362247 (96.75)	128591 (96.94)	73902 (97.02)	54837 (97.18)	
Ex	659 (1.68)	1900 (1.47)	3423 (1.1)	3600 (1.07)	3654 (0.98)	1240 (0.93)	656 (0.86)	467 (0.83)	
Current	2002 (5.12)	5038 (3.89)	9379 (3.03)	8872 (2.64)	8533 (2.28)	2821 (2.13)	1615 (2.12)	1123 (1.99)	
Drinking (%)									<.001
Non	33702 (86.13)	111638 (86.25)	269710 (87.05)	293860 (87.47)	331263 (88.47)	117469 (88.55)	67958 (89.22)	50422 (89.36)	
Mild	5244 (13.4)	17191 (13.28)	38649 (12.47)	40338 (12.01)	41297 (11.03)	14516 (10.94)	7801 (10.24)	5652 (10.02)	
Heavy	181 (0.46)	599 (0.46)	1488 (0.48)	1762 (0.52)	1874 (0.5)	667 (0.5)	414 (0.54)	353 (0.63)	
Income* (%)	7411 (18.94)	24913 (19.25)	59378 (19.16)	64611 (19.23)	70659 (18.87)	24606 (18.55)	14153 (18.58)	10505 (18.62)	<.001
RVO (%)	513 (1.31)	1857 (1.43)	5563 (1.8)	6890 (2.05)	9020 (2.41)	3258 (2.46)	1942 (2.55)	1515 (2.68)	<.001
RVO duration (yr)	9.41 (9.15;9.62)	9.41 (9.15;9.64)	9.42 (9.14;9.68)	9.41 (9.13;9.68)	9.42 (9.12;9.72)	9.43 (9.11;9.72)	9.44 (9.10;9.75)	9.44 (9.07;9.77)	<.001

BMI = body mass index, CKD = chronic kidney disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HRT = hormone replacement therapy, HTN = hypertension, RVO = retinal vein occlusion, SBP = systolic blood pressure, TC = total cholesterol, WC = waist circumference.
* low income 25%.

women group, the HR of RVO increased with an increase in diastolic blood pressure from <70 mm Hg to 85 to 90 mm Hg, and no significant elevation in the HR of RVO was observed with an increase in diastolic blood pressure from 90 to 95 mm Hg to ≥100 mm Hg.

3.4. Association between the use of medications and the development of retinal vein occlusion

In this study, we further analyzed the effect of each class of medication. We confirmed that the prescription of medications was higher in the postmenopausal group than the premenopausal group in Supplementary Digital Content Table 1, http://links.lww.com/MD/G460. It is known that doctors tend to prefer angiotensin receptor blockers to angiotensin-converting enzyme inhibitors as their primary anti-hypertension drug due to side effects of angiotensin-converting enzyme inhibitors, such as dry cough, and similar trends were found in this study. In a fully adjusted Cox proportional hazard model, all antihypertensive agents except angiotensin-converting enzyme inhibitors, DM medications, and dyslipidemia medications showed statistical significance. Additionally, P2Y12 inhibitor showed statistical

Table 4

Incidence rate of retinal vein occlusion in pre-menopausal and post-menopausal women by levels of systolic blood pressure.

	Pre-menopausal women				Post-menopausal women			
SBP (mm Hg)	No. of patients	Events	Duration (person-year)	IR	No. of patients	Events	Duration (person-year)	IR
< 100	83876	281	781340.22	0.360	39127	513	360359.5	1.424
100-110	234236	903	2179334.93	0.414	129428	1857	1192443.21	1.557
110-120	351566	1800	3268227.97	0.551	309847	5563	2841153.43	1.958
120-130	262925	1677	2440048.53	0.687	335960	6890	3070312.49	2.244
130-140	163866	1426	1517874.24	0.939	374434	9020	3400268.02	2.653
140-150	38685	439	357810.7	1.227	132652	3258	1200376.07	2.714
150-160	18281	217	168896.74	1.285	76173	1942	687090.53	2.826
≥ 160	11723	189	107907.65	1.752	56427	1515	502725.13	3.014

IR = incidence rate, No. = number, SBP = systolic blood pressure.

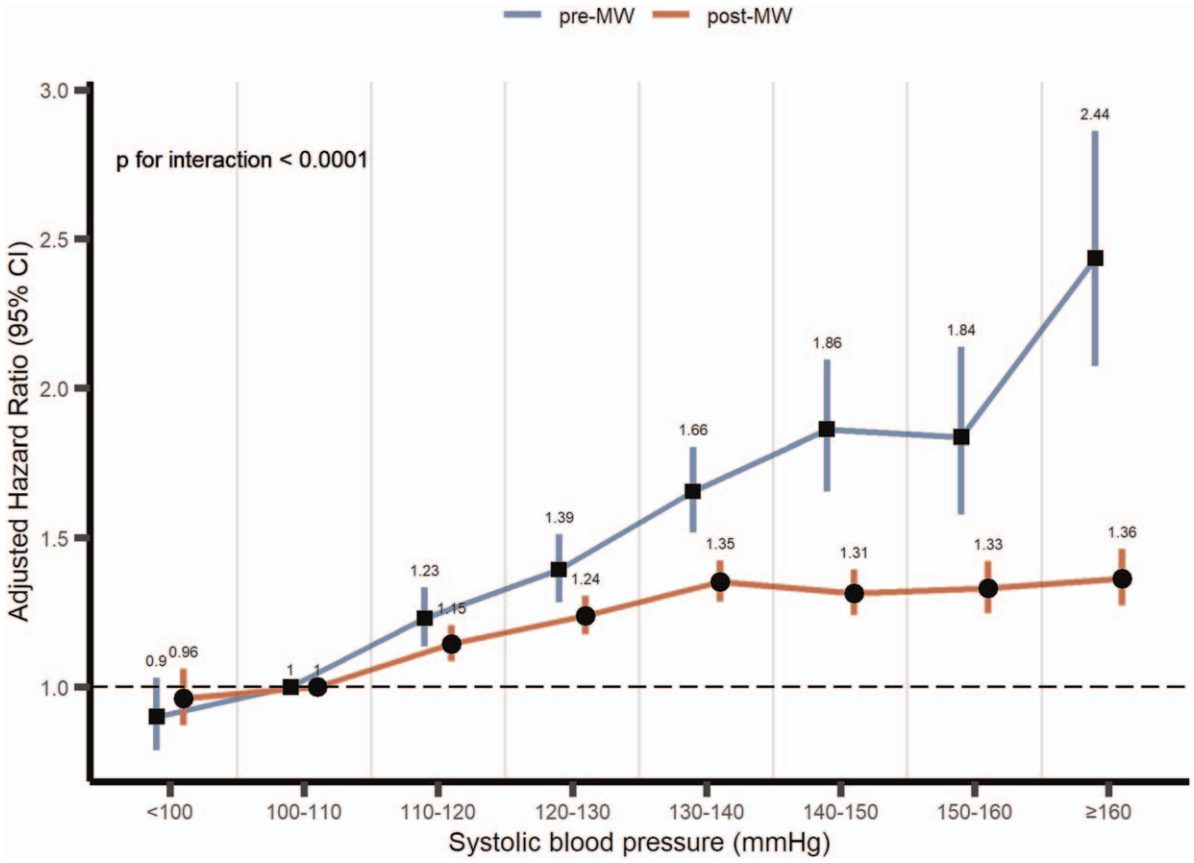

Figure 2. Adjusted hazard ratios of systolic blood pressure for RVO by menopause. The risk of RVO development in pre-menopausal women increased steadily with elevation of systolic blood pressure; however, it did not in post-menopausal women. The model was adjusted for age, sex, smoking status, alcohol consumption, body mass index, regular physical exercise, low income, diabetes mellitus, dyslipidemia, chronic kidney disease, and use of antihypertensive medication. MW = menopausal women, RVO = retinal vein occlusion.

significance in the postmenopausal group but not in the premenopausal group. Aspirin did not show any statistical significance in this study. The detailed results are summarized in Supplementary Digital Content Table 2, http://links.lww.com/MD/G460. Furthermore, we performed subgroup analyses by hormone replacement therapy in the postmenopausal women group. There was no significant difference between both groups, and elevated blood pressure was associated with both groups (Supplementary Digital Content Table 3, http://links.lww.com/MD/G460).

4. Discussion

In this nationwide study, the incidence of RVO was higher in the postmenopausal women group than in the premenopausal women group. Cox proportional hazard models were adjusted for socioeconomic and clinical variables and showed a statistically significant association between blood pressure and the development of RVO in both the pre- and postmenopausal women groups. Notably, blood pressure presented a higher HR for development of RVO in the premenopausal women group than in the postmenopausal women group.

Table 5

Incidence rate of retinal vein occlusion in pre-menopausal and post-menopausal women by levels of diastolic blood pressure.

	Pre-menopausal women				Post-menopausal women			
DBP (mm Hg)	No. of patients	Events	Duration (person-year)	IR	No. of patients	Events	Duration (person-year)	IR
<70	379206	1531	3526521.03	0.43414	261226	4197	2392956.2	1.7539
70-75	309266	1616	2874974.83	0.56209	334012	6550	3052823.47	2.14555
75-80	129887	781	1205448.82	0.64789	172535	3596	1576742.07	2.28065
80-85	216589	1620	2010035.9	0.80596	382215	8700	3476819.36	2.50229
85-90	61478	549	568988.52	0.96487	118850	2956	1080865.4	2.73485
90-95	41652	472	385612.93	1.22403	118798	2839	1075217.95	2.64039
95-100	9289	110	85775.91	1.28241	19543	480	177484.67	2.70446
≥100	17791	253	164083.04	1.5419	46869	1240	421819.25	2.93965

DBP = diastolic blood pressure, IR = incidence rate, No. = number.

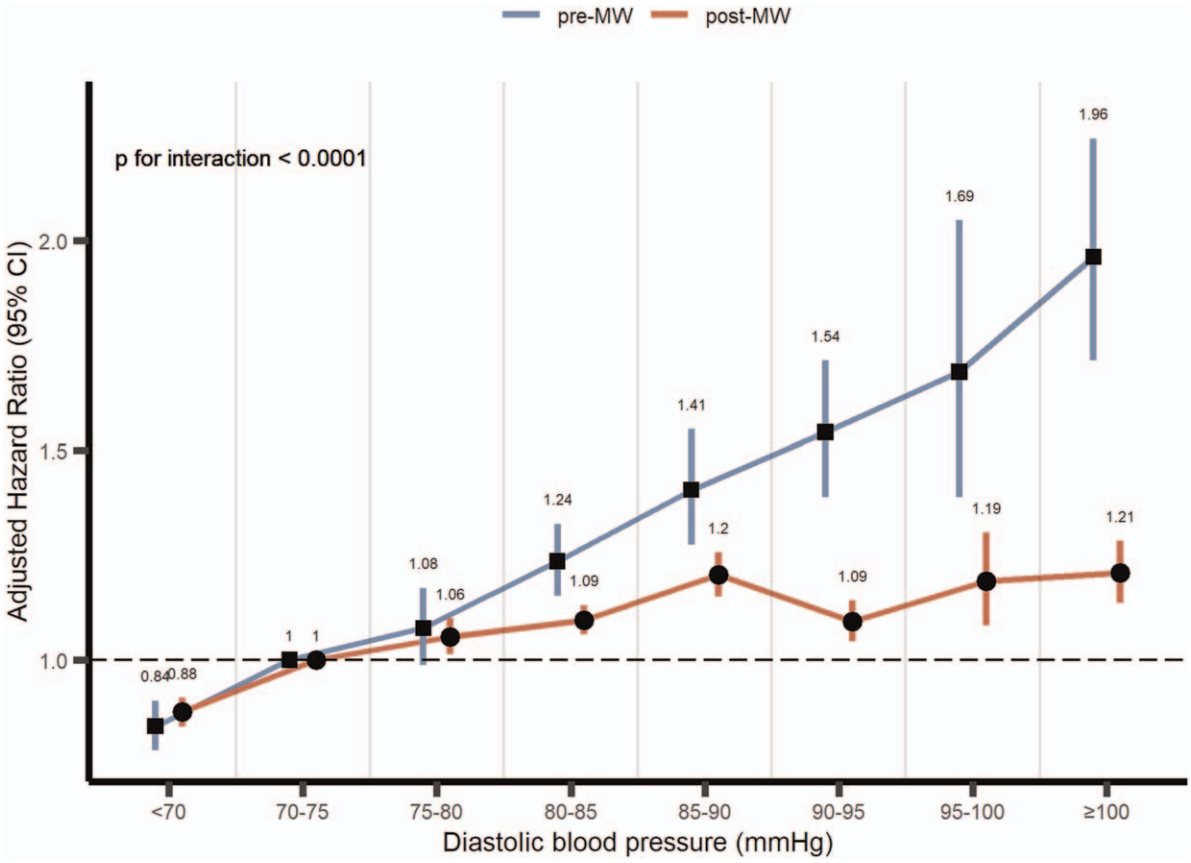

Figure 3. Adjusted hazard ratios of diastolic blood pressure for RVO by menopause. The risk of RVO development in pre-menopausal women increased steadily with elevation of diastolic blood pressure; however, it did not in post-menopausal women. The model was adjusted for age, sex, smoking status, alcohol consumption, body mass index, regular physical exercise, low income, diabetes mellitus, dyslipidemia, chronic kidney disease, and use of antihypertensive medication. MW = menopausal women, RVO = retinal vein occlusion.

Hypertension has been identified as a risk factor for RVO in several studies, including the Beijing Eye Study,[23] Beaver Dam Eye Study,[1] and Blue Mountains Eye Study.[11] To date, the pathophysiology of RVO and hypertension has not been fully described, although several mechanisms have been proposed. First, elevated blood pressure can directly damage the retinal blood vessels causing hemorrhages, cotton wool spots, and macular edema.[24] Second, systemic hypertension has been demonstrated to adversely affect the ocular structure in various hypertensive eye diseases.[25] For example, systemic hypertension is associated with fewer perifoveal arterioles and venules[26] and alteration of retinal vascular structures.[27] Chronic hypertension can as well cause sclerosis of the arterioles, leading to increased vascular resistance and reduced blood perfusion.[28] Moreover, hypertension is related to increased intraocular pressure and abnormalities of retinal microvasculature.[29] In addition, the renin-angiotensin-aldosterone system is known to be involved in the pathogenesis of ocular diseases.[30]

In this study, increased systolic and diastolic blood pressures showed a higher HR for RVO in the premenopausal women group than that in the postmenopausal women group. The prevalence of hypertension in women increases during the menopausal transition period.[31] A previous study described that the increased prevalence of hypertension was influenced by endothelial dysfunction and sympathetic activation in response to changes in sex hormones in women.[32] Sex hormones also exhibit vasodilator effect through endothelium-independent inhibition of vascular smooth muscle contraction and induce vasodilatation through NO-cGMP prostacyclin-cAMP pathways.[33] Estradiol decreased the vascular resistance by synthesis of endogenous vasodilator[34] and reduced synthesis of endogeneous vasocontrictor[35] and activation of potassium channels.[36] In adittion estradiol decrease basal sympathetic tonevascular tone and inhibit the vascular adhesion molecules (intercellular adhesion modeluce-1 and endothelial leukocyte adhesion molecule-1).[37] Similar effects were observed in progestin. These effects of sex hormones explain the lower prevalence of hypertension in young women compared to older women. Therefore, it could be concluded that the development of hypertension in young women is due to the various mechanism that offsets the antihypertensive effect of sex hormones. Based on this inference, we assumed that high blood pressure in young women leads to a worse prognosis than in elderly women. Additionally, the results of the multi-centered Pathological Determinants of Atherosclerosis in Youth study showed that blood pressure was associated with the extent of atherosclerosis in old and young patients.[38] Furthermore, the association between hypertension and the extent of atherosclerosis might explain the higher risk of RVO with higher blood pressure in the premenopausal women group than in the postmenopausal

women group. It is as well probable that the high blood pressure in younger patients is influenced by the presence of comorbidities that can elevate blood pressure in this group. Dyslipidemia is linked with venous thrombosis which might be related with RVO.[39,40] The previous study[41] also reported the association between reduced eGFR and RVO, though underlying pathophysiological mechanisms are still unclear. These comorbidities might be related with damage in retinal vasculartur by elevated blood pressure. This is supported by our findings of a higher prevalence of comorbidities with increasing blood pressure in both pre- and postmenopausal women, as shown in Tables 2 and 3. The postmenopausal women group was older and had higher dyslipidemia, obesity, abdominal obesity, diabetes mellitus and CKD than premenopausal women group (Table 1) and these factors are known risk factors for RVO. The lowering of the influence of hypertension in postmenopausal women is thought to be due to the relatively high prevalence of comobidity, which will might eventually lead to a difference in the prevalence of RVO in women before and after menopause.

To the best of our knowledge, this is the first study to report that the effect of hypertension on risk of RVO varies with menopause. Although our study has several strengths, including a large-scale, nationwide observational design, robust data collection, validated follow-up duration (approximately 9 years), and separate analyses of both systolic and diastolic blood pressure, it also has some limitations. First, as in all observation studies, we could not assess causality between blood pressure and the development of RVO. However, observational studies are powerful tools for assessing epidemiologic relationships, and we utilized complementary analytic methods to robustly examine the effect of blood pressure and relevant clinical outcomes.[42] Second, despite data from men was required to analyze the effects of age, comorbidity and sex hormone on RVO, we could not analyze inforomation of men because of limitation of database which was consists of only women. Third, we could not control all potential confounding factors and hidden biases. Socioeconomic status and smoking intensity are well known to be closely related with cancer development, and adjustment for these factors was insufficient due to limited data on these variables in this study. Fourth, because our study is a retrospective one using data from a registry, there is a possibility that bias occurred due to overdiagnosis/underdiagnosis or misclassification of patients. Fifth, we could not distinguish the indivisuals who changed to menopause during the follow-up period. Fianlly, we could not distinguish between the subtypes of RVO, because there is no way to distinguish between BRVO and CRVO in this study with ICD-10 code.

In summary, higher blood pressure was found to be associated with an increased risk of RVO in premenopausal women, and this risk is higher in premenopausal women compared to postmenopausal women. This suggests that comprehensive management of hypertension in premenopausal women is necessary to reduce the risk of RVO.

Author contributions

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