Hypertension

ORIGINAL ARTICLE

Effects of Blood Pressure According to Age on End-Stage Renal Disease Development in Patients With Diabetes: A Nationwide Population-Based Cohort Study

Eun Hui Bae, Sang Yeob Lim, Bongseong Kim, Tae Ryom Oh, Su Hyun Song, Sang Heon Suh, Hong Sang Choi, Eun Mi Yang, Chang Seong Kim, Seong Kwon Ma, Kyung-Do Han,* Soo Wan Kim*

BACKGROUND: Recent hypertension guidelines have recommended lower blood pressure (BP) targets in high-risk patients. However, there are no specific guidelines based on age or systolic and diastolic blood pressure (SBP and DBP, respectively). We aimed to assess the effects of age-related BP on development of end-stage renal disease (ESRD) in patients with diabetes.

METHODS: A total of 2 563 870 patients with diabetes aged >20 years were selected from the Korean National Health Screening Program from 2009 to 2012 and followed up until the end of 2019. Participants were categorized into age and BP groups, and the hazard ratios for ESRD were calculated.

RESULTS: During a median follow-up of 7.15 years, the incidence rates of ESRD increased with increasing SBP and DBP. The hazard ratio for ESRD was the highest in patients younger than 40 years of age with DBP≥100 mm Hg. The effect of SBP and DBP on ESRD development was attenuated with age (interaction *P* was <0.0001 for age and SBP, and 0.0022 for age and DBP). The subgroup analysis for sex, antihypertension medication, and history of chronic kidney disease showed higher hazard ratios for ESRD among males, younger than 40 years, not taking antihypertension medications and chronic kidney disease compared to those among females, older than 40 years, antihypertension medication, and nonchronic kidney disease groups.

CONCLUSIONS: Higher SBP and DBP increase the risk of developing ESRD in patients with diabetes, and in particular, younger individuals face greater risk. Therefore, intensive BP management is warranted in younger patients to prevent ESRD. **(*Hypertension*. 2022;79:1765–1776. DOI: 10.1161/HYPERTENSIONAHA.121.18881.)** • **Supplemental Material**

Key Words: blood pressure ■ cardiovascular diseases ■ hypertension ■ kidney diseases ■ young adult

Diabetes is a strong risk factor for end-stage renal disease (ESRD).[1] Hypertension also plays a crucial role in the development and progression of kidney failure.[2,3] Blood pressure (BP) rises with declining kidney function which in turn aggravates hypertension. Moreover, as chronic kidney disease (CKD) worsens, BP becomes more difficult to control, propagating a vicious cycle of worsening BP and renal function. Therefore, early diagnosis and prompt treatment of hypertension in high-risk patients are crucial. In addition, hypertension is common among young people and can cause harmful health effects even at a young age.[4]

In recent hypertension guidelines, lower BP targets are recommended for high-risk patients, such as those

Correspondence to: Kyung-Do Han, Department of Statistics and Actuarial Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Korea, Email hkd917@naver.com or Soo Wan Kim, Department of Internal Medicine, Chonnam National University Medical School, 42 Jebongro, Gwangju 61469, Korea, Email skimw@chonnam.ac.kr
*K.D. Han and S.W. Kim contributed equally.
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NOVELTY AND RELEVANCE

What Is New?

This is the first study demonstrating the effects of age-related blood pressure (BP) and end-stage renal disease (ESRD) development in patients with diabetes using a well-established and validated longitudinal national database.

The hazard ratio for ESRD was the highest in patients younger than 40 years of age with diastolic BP≥100 mm Hg, and the effects of BP on ESRD development were prominent in males, younger than 40 years, not taking antihypertension medications and chronic kidney disease compared to those among females, older than 40 years, antihypertension medication and non–chronic kidney disease groups.

The effect of systolic BP and diastolic BP on ESRD development was attenuated with age.

What Is Relevant?

The 2017 American College of Cardiology/American Heart Association guidelines have recommended lower BP target in high-risk patients such as diabetes or chronic kidney disease, but the effect of age-based BP on ESRD development in patients with diabetes was not elucidated.

Clinical/Pathophysiological Implications?

Higher systolic BP and diastolic BP increase the risk of developing ESRD in patients with diabetes, and in particular, younger individuals face greater risk. Therefore, intensive BP management is warranted in younger patients to prevent ESRD.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CKD	chronic kidney disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
ESRD	end-stage renal disease
HR	hazard ratio
ICD-10	*International Statistical Classification of Diseases, Tenth Revision*
KNHIS	Korean National Health Insurance Service
SBP	systolic blood pressure

with renal disease or diabetes.[5] However, the effects of BP on the development of ESRD according to age in patients with diabetes have not been investigated. In addition, a recent study identified numerous barriers to good BP control in young adults.[6]

Therefore, this nationwide population-based study aimed to investigate the association between BP categories according to age and the risk of ESRD among patients with diabetes using the Korean National Health Insurance Service (KNHIS) database.

METHODS

KNHIS Data

In this study, we used the national health insurance claims database established by the KNHIS, which includes all claims data provided by the KNHIS and Medical Aid programs. The KNHIS database is considered to represent the entire South Korean population, and the details of this database have been previously described.[7] Depending on their occupations, all insured Koreans undergo an annual or biennial health examination that is supported by the KNHIS. The sociodemographic data and all medical expenses for both inpatient and outpatient services, pharmacy dispensing claims, and mortality information are included in the database. Anonymized data are publicly available from the National Health Insurance Sharing Service and can be accessed at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

This study was approved by the institutional review board of Chonnam National University Hospital, Korea (CNUH-EXP-2021-289) informed consent was waived and was performed in accordance with the ethical standards of the committee responsible for human experimentation and the Helsinki Declaration of 1975, as revised in 2013.

Subjects

Initially, 2 746 079 patients with diabetes who underwent health checkups from 2009 to 2012 were identified. Of these, we included patients who had undergone a repeat health checkup after 2 years. The index date was the date of the last health check-up. We excluded those aged <20 years because ESRD development is rare in this subpopulation. We also excluded subjects with malignancy or a history of ESRD before the index date and those with missing health examination data. Finally, 2 563 870 subjects with diabetes were included in the study. Systolic blood pressure (SBP) values from <100 to ≥160 mm Hg were divided into 5 groups at 20 mm Hg intervals, and DBP values from <70 to ≥110 mm Hg were divided into 6 groups at 10 mm Hg intervals. The detailed flowchart of the selection of study subjects is presented in Figure S1. The participants were followed up until one of the following occurred: a new diagnosis of ESRD, death, loss of health insurance qualification, or end of the study (December 31, 2019).

Definitions

Patients with diabetes were defined as follows: (1) having at least one claim per year for a prescription of antidiabetic

Table 1. Baseline Characteristics of Subjects According to the Incident ESRD

Variable	None ESRD (N=2 537 790)	ESRD (N=26 580)	*P* value	ASD
Age	57.36±12.37	60.97±11.15	<0.0001	0.306
Age group			<0.0001	
20s	35 846 (1.41)	192 (0.72)		0.0951
30s	159 595 (6.29)	671 (2.52)		0.2609
40s	461 749 (18.2)	3239 (12.19)		0.2376
50s	732 459 (28.87)	6828 (25.69)		0.101
60s	673 610 (26.55)	8892 (33.45)		0.2135
70s	474 031 (18.68)	6758 (25.43)		0.231
Sex (male), %	1 520 300 (59.92)	17 235 (64.84)	<0.0001	0.1438
Smoking			<0.0001	
Never	1 411 859 (55.64)	14 643 (55.09)		0.0156
Ex	466 818 (18.4)	5462 (20.55)		0.0768
Current	658 613 (25.96)	6475 (24.36)		0.0522
Drinking			<0.0001	
None	1 449 838 (57.14)	18 633 (70.1)		0.3845
Moderate	833 634 (32.86)	6273 (23.6)		0.2925
Heavy*	253 818 (10)	1674 (6.3)		0.1917
Income-low†	531 120 (20.93)	6377 (23.99)	<0.0001	0.1038
PA-regular	521 065 (20.54)	5186 (19.51)	<0.0001	0.0364
Systolic BP	128.97±15.78	134.6±18.97	<0.0001	0.323
Diastolic BP	79.05±10.27	79.57±11.58	<0.0001	0.0475
Hypertension	1 171 500 (46.17)	21 056 (79.22)	<0.0001	1.0284
Dyslipidemia	1 053 471 (41.52)	15 799 (59.44)	<0.0001	0.5152
Antihypertension medication number			<0.0001	
0	1 365 790 (53.83)	5524 (20.78)		1.0284
1	665 477 (26.23)	7613 (28.64)		0.0764
2	384 634 (15.16)	7929 (29.83)		0.5047
3	104 963 (4.14)	4115 (15.48)		0.5492
4	14 855 (0.59)	1161 (4.37)		0.3463
≥5	1571 (0.06)	238 (0.89)		0.171
Antihypertension medication type			<0.0001	
Alpha blocker	28 404 (1.12)	1255 (4.72)	<0.0001	0.3041
ACE inhibitor	141 640 (5.58)	4076 (15.33)	<0.0001	0.4565
ARB	802 640 (31.63)	17 089 (64.29)	<0.0001	0.9783
Beta blocker	282 195 (11.12)	7201 (27.09)	<0.0001	0.5867
CCB	529 698 (20.88)	10 952 (41.2)	<0.0001	0.6367
Diuretics	25 177 (0.99)	656 (2.47)	<0.0001	0.1608
Others	7266 (0.29)	453 (1.7)	<0.0001	0.2014
WC, cm	85.43±8.89	86.05±9.2	<0.0001	0.1113
BMI, kg/m^2	25.07±3.67	24.68±3.51	<0.0001	0.0684
BMI_5 level			<0.0001	
<18.5	40 416 (1.59)	589 (2.22)		0.0652
18.5–23	630 023 (24.83)	7926 (29.82)		0.1586
23–25	628 821 (24.78)	6562 (24.69)		0.0029
25–30	1 041 399 (41.04)	9616 (36.18)		0.1413
≥30	196 631 (7.75)	1887 (7.1)		0.0351
CKD	285 389 (11.25)	15 938 (59.96)	<0.0001	1.6709
MI	29 576 (1.17)	732 (2.75)	<0.0001	0.1615
Stroke	124 822 (4.92)	2872 (10.81)	<0.0001	0.3113
CHF	50 156 (1.98)	1537 (5.78)	<0.0001	0.2796
Insulin user	208 309 (8.21)	19 181 (72.16)	<0.0001	1.138
Diabetes ≥5 y	765 905 (30.19)	7562 (28.45)	<0.0001	0.9251
OHA≥3	361 482 (14.25)	161.61±78.82	<0.0001	0.3519
Glucose, mg/dL	144.6±46.46	196.52±56.31	<0.0001	0.2629
TC, mg/dL	196.85±46.04	49.62±31.45	0.2556	0.0063
HDL, mg/dL	52.27±29.32			0.087
LDL, mg/dL	112.69±84.44	112.44±107.6	0.6384	0.0025
Creatinine, mg/dL	1.02±1.07	1.7±2.06	<0.0001	0.4141
eGFR (CKD-EPI)		55.09±26.95	<0.0001	1.1623

(*Continued*)

eGFR <60 mL/(min·1.73 m^2) using CKD-EPI formula. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASD, absolute standardized difference; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease, CKD-EPI, CKD Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; OHA, oral hypoglycemic agents; PA, physical activity; TC, total cholesterol; and WC, waist circumference.

*Alcohol consumption ≥30 g/d.

†Low income 25%.

medication under the *International Statistical Classification of Diseases*, *Tenth Revision* (*ICD-10*) codes E11 to E14 from the insurance claims data, or (2) having a fasting plasma glucose ≥126 mg/dL in the health examination without a prescription for antidiabetic medication.[7] Antidiabetic medications included sulfonylureas, metformin, dipeptidyl-peptidase 4 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, and insulins. Comorbidities were defined using *ICD-10* diagnosis codes with health care usage and medication or health examination results, as in the previous studies.[8-10] Hypertension was defined as a previous diagnosis of hypertension according to the *ICD-10, Clinical Modification* codes (I10–I13, I15) or a recorded systolic BP (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg. BP was measured by trained clinicians at least twice using mercury or automatic sphygmomanometer in a sitting position, following a minimum of 5 min of rest in the appropriate position, after obtaining the anthropometric measurements. CKD was defined as an estimated glomerular filtration rate <60 mL/(min·1.73 m^2) and was calculated using CKD Epidemiology Collaboration equation.[11] Dyslipidemia was defined as a presence of *ICD-10, Clinical Modification* code E78, and history of lipid-lowering drug use or a total serum cholesterol concentration of ≥240 mg/dL in the health examination data. Congestive heart

Table 2. Baseline Characteristics of Study Population by SBP Group

Variables	SBP<100 (N=31 874)	SBP<120 (N=578 750)	SBP<140 (N=1 367 969)	SBP<160 (N=460 020)	SBP≥160 (N=125 257)	*P* value
Age	55.97±12.11	55.67±12.29	57.02±12.39	59.89±11.9	60.79±12.18	<0.0001
Age group						<0.0001
20s	720 (2.26)	11 791 (2.04)	19 676 (1.44)	3096 (0.67)	755 (0.6)	
30s	1580 (4.96)	39 782 (6.87)	93 353 (6.82)	20 239 (4.4)	5312 (4.24)	
40s	6593 (20.68)	122 190 (21.11)	254 442 (18.6)	64 858 (14.1)	16 905 (13.5)	
50s	10 673 (33.48)	179 787 (31.06)	396 402 (28.98)	121 944 (26.51)	30 481 (24.33)	
60s	7628 (23.93)	139 684 (24.14)	358 340 (26.2)	139 593 (30.34)	37 257 (29.74)	
70s	4680 (14.68)	85 516 (14.78)	245 756 (17.97)	110 290 (23.98)	34 547 (27.58)	
Sex (male), %	14 906 (46.77)	330 007 (57.02)	846 317 (61.87)	273 631 (59.48)	72 674 (58.02)	<0.0001
Smoking						<0.0001
Never	19 276 (60.48)	323 613 (55.92)	743 234 (54.33)	265 416 (57.7)	74 963 (59.85)	
Ex	4583 (14.38)	97 766 (16.89)	259 514 (18.97)	88 812 (19.31)	21 605 (17.25)	
Current	8015 (25.15)	157 371 (27.19)	365 221 (26.7)	105 792 (23)	28 689 (22.9)	
Drinking						<0.0001
None	22 394 (70.26)	353 579 (61.09)	765 066 (55.93)	257 799 (56.04)	69 633 (55.59)	
Moderate	8031 (25.2)	181 490 (31.36)	463 593 (33.89)	147 521 (32.07)	39 272 (31.35)	
Heavy*	1449 (4.55)	43 681 (7.55)	139 310 (10.18)	54 700 (11.89)	16 352 (13.05)	
Income-low†	7289 (22.87)	121 976 (21.08)	281 558 (20.58)	98 192 (21.35)	28 482 (22.74)	<0.0001
PA-regular	6236 (19.56)	117 852 (20.36)	284 461 (20.79)	94 011 (20.44)	23 691 (18.91)	<0.0001
Systolic BP	93.02±4.34	111.06±5.51	128.27±6	145.79±5.44	167.93±10.46	<0.0001
Diastolic BP	60.52±5.98	70.16±6.72	78.95±6.96	87.23±8.9	96.09±11.65	<0.0001
Antihypertensive medication number						<0.0001
0	22 919 (71.91)	383 782 (66.31)	754 724 (55.17)	171 384 (37.26)	38 505 (30.74)	
1	5361 (16.82)	118 185 (20.42)	354 838 (25.94)	153 821 (33.44)	40 885 (32.64)	
2	2648 (8.31)	59 632 (10.3)	198 798 (14.53)	100 088 (21.76)	31 397 (25.07)	
3	824 (2.59)	14 920 (2.58)	51 707 (3.78)	29 675 (6.45)	11 952 (9.54)	
4	110 (0.35)	2014 (0.35)	7146 (0.52)	4535 (0.99)	2211 (1.77)	
≥5	12 (0.04)	217 (0.04)	756 (0.05)	517 (0.11)	307 (0.24)	
Antihypertensive medication type						<0.0001
Alpha blocker	337 (1.06)	5235 (0.9)	14 981 (1.1)	6937 (1.51)	2169 (1.73)	
ACE inhibitor	1431 (4.49)	25 423 (4.39)	74 321 (5.43)	33 712 (7.33)	10 829 (8.65)	
ARB	6423 (20.15)	134 915 (23.31)	417 190 (30.5)	198 770 (43.21)	62 431 (49.84)	
Beta blocker	2387 (7.49)	45 042 (7.78)	142 440 (10.41)	73 433 (15.96)	26 094 (20.83)	
CCB	2776 (8.71)	75 336 (13.02)	274 430 (20.06)	142 708 (31.02)	45 400 (36.25)	
Diuretics	228 (0.72)	4338 (0.75)	13 183 (0.96)	6169 (1.34)	1915 (1.53)	
Others	49 (0.15)	1074 (0.19)	3417 (0.25)	2065 (0.45)	1114 (0.89)	
MI	620 (1.95)	7405 (1.28)	15 187 (1.11)	5458 (1.19)	1638 (1.31)	
Stroke	1638 (5.14)	25 283 (4.37)	64 995 (4.75)	27 488 (5.98)	8290 (6.62)	
CHF	1047 (3.28)	12 136 (2.1)	25 614 (1.87)	9843 (2.14)	3053 (2.44)	
WC, cm	79.67±9.83	83.24±8.71	85.72±8.7	87.21±8.89	87.35±8.99	<0.0001
BMI, kg/m^2	22.87±3.19	24.27±3.24	25.18±3.34	25.71±4.75	25.75±3.74	<0.0001
BMI 5 level						<0.0001
<18.5	2253 (7.07)	15 156 (2.62)	17 473 (1.28)	4563 (0.99)	1560 (1.25)	
18.5–23	14 872 (46.66)	186 928 (32.3)	320 748 (23.45)	90 009 (19.57)	25 392 (20.27)	
23–25	7224 (22.66)	150 668 (26.03)	342 028 (25)	107 099 (23.28)	28 364 (22.64)	
25–30	6820 (21.4)	198 803 (34.35)	581 084 (42.48)	209 390 (45.52)	54 918 (43.84)	
≥30	705 (2.21)	27 195 (4.7)	106 636 (7.8)	48 959 (10.64)	15 023 (11.99)	

(*Continued*)

Table 2. Continued

Variables	SBP<100 (N=31 874)	SBP<120 (N=578 750)	SBP<140 (N=1 367 969)	SBP<160 (N=460 020)	SBP≥160 (N=125 257)	*P* value
Hypertension	8955 (28.09)	194 968 (33.69)	613 245 (44.83)	288 636 (62.74)	86 752 (69.26)	<0.0001
Dyslipidemia	12 492 (39.19)	231 494 (40)	568 366 (41.55)	202 460 (44.01)	54 458 (43.48)	<0.0001
CKD	4155 (13.04)	60 544 (10.46)	153 756 (11.24)	63 087 (13.71)	19 785 (15.8)	<0.0001
Insulin user	4594 (14.41)	55 648 (9.62)	109 925 (8.04)	38 093 (8.28)	10 729 (8.57)	<0.0001
Diabetes ≥5 y	11 411 (35.8)	179 340 (30.99)	409 349 (29.92)	145 997 (31.74)	38 989 (31.13)	<0.0001
OHA≥3	5696 (17.87)	90 018 (15.55)	193 078 (14.11)	63 903 (13.89)	16 349 (13.05)	<0.0001
Glucose, mg/dL	145.14±55.87	144.46±48.66	144.48±46.19	144.87±45.48	149.16±49.42	<0.0001
TC, mg/dL	185.34±44.28	192.53±44.12	197±46.26	200.31±46.76	205.31±49.81	<0.0001
HDL, mg/dL	52.32±26.53	52.04±27.63	52.06±28.53	52.63±33.02	53.6±31.86	<0.0001
LDL, mg/dL	108.71±93.28	111.52±78.56	112.58±82.29	113.76±90.12	116.34±111.09	<0.0001
Creatinine, mg/dL	1.01±1.01	1.01±1.03	1.04±1.12	1.02±1.07	1.03±1.11	<0.0001
eGFR (CKD-EPI)	82.99±22.02	83.74±20.36	82.78±20.43	80.73±20.3	79.63±20.85	<0.0001

eGFR <60 mL/(min·1.73 m^2) using CKD-EPI formula. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease, CKD-EPI, CKD Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; OHA, oral hypoglycemic agents; PA, physical activity; SBP, systolic BP; TC, total cholesterol; and WC, waist circumference.

*Alcohol consumption ≥30 g/d.

†Low income 25%.

failure was defined as *ICD-10, Clinical Modification* code I50 diagnosed at least once in the year based on the index date, regardless of outpatient visit or inpatient hospitalization. A low income was defined as the lowest 20% of socioeconomic status. Body mass index was calculated as the weight (in kilograms) divided by the height (in meters squared). Subjects were categorized into 5 groups according to body mass index: underweight (<18.5 kg/m^2), normal weight (18.5–22.9 kg/m^2), overweight (23–24.9 kg/m^2), obese stage I (25–29.9 kg/m^2), and obese stage II (≥30 kg/m^2), according to World Health Organization recommendations for Asians. Smoking history was categorized as never, ex, or current smoker. Alcohol consumption was categorized into none, moderate, or heavy drinkers (≥30 g of alcohol per day). Regular exercise was defined as moderate physical activity for at least 20 min per day over >5 days during the last week.

Outcomes

The end point of the study was incident ESRD, which was defined using a combination of *ICD-10* codes (N18–19, Z49, Z94.0, and Z99.2) and a special code (V code) that was assigned in the initiation of renal replacement therapy (hemodialysis, V001; peritoneal dialysis, V003) or kidney transplantation (V005) during hospitalization. All medical expenses for dialysis are reimbursed using the Korean Health Insurance Review and Assessment Service database. These patients are also registered as special medical aid beneficiaries. Therefore, we were able to identify every patient with ESRD in the entire South Korean population and were able to analyze the data for all patients with ESRD who underwent dialysis. Codes for treatment or medical expense claims included V005 for kidney transplantation, V001 for hemodialysis, and V003 for peritoneal dialysis. We excluded individuals without previous CKD who had a transplant or dialysis code on the same date as an acute renal failure code. Subjects on continuous renal replacement therapy or acute peritoneal dialysis were also excluded.

Statistical Analyses

Data are presented as the mean±SD for continuous variables and numbers with proportions for categorical variables. Nonnormally distributed variables are presented as geometric means (95% CI). Intergroup differences were tested using a χ^2 test or ANOVA, as appropriate. The incidence rates of ESRD are presented per 1000 person-years. The absolute standardized difference, which is unaffected by the population number (unlike *P*), was calculated since the number of participants in the study was large. Multivariable Cox proportional hazard regression analysis was used to estimate the hazard ratios (HRs) and 95% CIs of the risk of ESRD associated with BP along with adjustment for age, sex, smoking, alcohol consumption, regular exercise, low-income status, use of insulin, number of oral hypoglycemic agents, duration of diabetes, previous history of hypertension and dyslipidemia, estimated glomerular filtration rate, antihypertension medication numbers and type, myocardial infarction, stroke, and congestive heart failure. In addition, subgroup analyses were performed in patients with diabetes according to sex, antihypertensive medication, and history of CKD. All data analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC), and P<0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

Table 1 shows the baseline characteristics of the participants with respect to the development of ESRD. Of the total population, 26 580 (1.04%) patients (median follow-up of 7.15 years) developed ESRD. The mean age of those who developed ESRD was higher than that of those who did not (60.97±11.15 years versus 57.36±12.37 years, respectively; p<0.001). The proportion of men (64.84%) and low-income

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Table 3. Baseline Characteristics of Study Population by DBP Group

Variables	DBP<70 (N=322 176)	DBP<80 (N=806 626)	DBP<90 (N=1 006 786)	DBP<100 (N=305 817)	DBP<110 (N=97 580)	DBP≥110 (N=24 885)	*P* value
Age	59.4±12.51	57.63±12.4	56.72±12.35	57.75±11.89	55.69±12.25	53.82±12.54	<0.0001
Age group							<0.0001
20s	5268 (1.64)	12 914 (1.6)	14 266 (1.42)	2268 (0.74)	1021 (1.05)	301 (1.21)	
30s	14 595 (4.53)	48 759 (6.04)	70 373 (6.99)	16 405 (5.36)	7517 (7.7)	2617 (10.52)	
40s	47 172 (14.64)	139 359 (17.28)	193 468 (19.22)	55 906 (18.28)	22 212 (22.76)	6871 (27.61)	
50s	83 587 (25.94)	228 564 (28.34)	298 004 (29.6)	92 528 (30.26)	29 559 (30.29)	7045 (28.31)	
60s	94 412 (29.3)	222 773 (27.62)	256 743 (25.5)	81 806 (26.75)	22 086 (22.63)	4682 (18.81)	
70s	77 142 (23.94)	154 257 (19.12)	173 932 (17.28)	56 904 (18.61)	15 185 (15.56)	3369 (13.54)	
Sex (male), %	162 242 (50.36)	462 374 (57.32)	635 594 (63.13)	193 248 (63.19)	66 465 (68.11)	17 612 (70.77)	<0.0001
Smoking							<0.0001
Never	197 148 (61.19)	461 530 (57.22)	540 050 (53.64)	166 649 (54.49)	49 197 (50.42)	11 928 (47.93)	
Ex	52 996 (16.45)	142 794 (17.7)	191 572 (19.03)	60 714 (19.85)	19 522 (20.01)	4682 (18.81)	
Current	72 032 (22.36)	202 302 (25.08)	275 164 (27.33)	78 454 (25.65)	28 861 (29.58)	8275 (33.25)	
Drinking							<0.0001
None	220 904 (68.57)	490 018 (60.75)	544 630 (54.1)	158 429 (51.81)	44 231 (45.33)	10 259 (41.23)	
Moderate	83 958 (26.06)	249 851 (30.97)	351 713 (34.93)	106 654 (34.88)	37 630 (38.56)	10 101 (40.59)	
Heavy*	17 314 (5.37)	66 757 (8.28)	110 443 (10.97)	40 734 (13.32)	15 719 (16.11)	4525 (18.18)	
Income-low†	67 333 (20.9)	167 972 (20.82)	209 306 (20.79)	65 687 (21.48)	21 541 (22.08)	5658 (22.74)	<0.0001
PA-regular	69 182 (21.47)	168 688 (20.91)	205 866 (20.45)	60 051 (19.64)	18 111 (18.56)	4353 (17.49)	<0.0001
Systolic BP	113.61±12.72	122.56±11.73	131.14±10.83	144.09±12.66	154.42±13.93	168.23±17.94	<0.0001
Diastolic BP	63.25±4.14	73.09±3.29	82.13±2.99	91.46±2.49	100.97±2.12	114.51±7.83	<0.0001
Antihypertensive medication number							<0.0001
0	189 471 (58.81)	463 610 (57.48)	539 391 (53.58)	127 827 (41.8)	40 948 (41.96)	10 067 (40.45)	
1	76 972 (23.89)	200 510 (24.86)	264 476 (26.27)	94 973 (31.06)	29 015 (29.73)	7144 (28.71)	
2	42 282 (13.12)	109 606 (13.59)	154 405 (15.34)	61 417 (20.08)	19 645 (20.13)	5208 (20.93)	
3	11 509 (3.57)	28 467 (3.53)	41 857 (4.16)	18 479 (6.04)	6729 (6.9)	2037 (8.19)	
4	1739 (0.54)	4012 (0.5)	5983 (0.59)	2786 (0.91)	1121 (1.15)	375 (1.51)	
≥5	203 (0.06)	421 (0.05)	674 (0.06)	335 (0.11)	122 (0.12)	54 (0.21)	
Antihypertensive medication type							<0.0001
Alpha blocker	4475 (1.39)	9053 (1.12)	10 855 (1.08)	3824 (1.25)	1152 (1.18)	300 (1.21)	
ACE inhibitor	17 419 (5.41)	42 476 (5.27)	56 767 (5.64)	20 991 (6.86)	6440 (6.6)	1623 (6.52)	
ARB	92 894 (28.83)	234 509 (29.07)	317 536 (31.54)	123 052 (40.24)	40 558 (41.56)	11 180 (44.93)	
Beta blocker	32 581 (10.11)	79 156 (9.81)	111 740 (11.1)	46 005 (15.04)	15 530 (15.92)	4384 (17.62)	<0.0001
CCB	52 709 (16.36)	148 716 (18.44)	216 463 (21.5)	87 149 (28.5)	28 176 (28.87)	7437 (29.89)	<0.0001
Diuretics	3189 (0.99)	7517 (0.93)	9973 (0.99)	3705 (1.21)	1139 (1.17)	310 (1.25)	<0.0001
Others	781 (0.24)	1876 (0.23)	2872 (0.29)	1373 (0.45)	604 (0.62)	213 (0.86)	<0.0001
MI	5179 (1.61)	9815 (1.22)	10 764 (1.07)	3347 (1.09)	947 (0.97)	256 (1.03)	<0.0001
Stroke	19 107 (5.93)	39 728 (4.93)	47 265 (4.69)	15 908 (5.2)	4562 (4.68)	1124 (4.52)	<0.0001
CHF	9021 (2.8)	16 423 (2.04)	18 168 (1.8)	5887 (1.93)	1720 (1.76)	474 (1.9)	<0.0001
BMI, kg/m^2	24.02±3.19	24.74±3.27	25.31±3.39	25.8±5.27	26.12±3.77	26.54±4.1	<0.0001
WC, cm	82.89±8.93	84.57±8.67	86.02±8.75	87.34±8.78	88.08±9.39	88.95±9.58	<0.0001
BMI 5 level							<0.0001
<18.5	9527 (2.96)	14 372 (1.78)	12 660 (1.26)	3098 (1.01)	1080 (1.11)	268 (1.08)	
18.5–23	112 489 (34.92)	221 658 (27.48)	225 458 (22.39)	57 567 (18.82)	16 786 (17.2)	3991 (16.04)	
23–25	84 543 (26.24)	209 407 (25.96)	246 636 (24.5)	69 138 (22.61)	20 853 (21.37)	4806 (19.31)	
25–30	102 855 (31.93)	312 715 (38.77)	436 825 (43.39)	141 872 (46.39)	45 280 (46.4)	11 468 (46.08)	
≥30	12 762 (3.96)	48 474 (6.01)	85 207 (8.46)	34 142 (11.16)	13 581 (13.92)	4352 (17.49)	

(*Continued*)

Table 3. Continued

Variables	DBP<70 (N=322 176)	DBP<80 (N=806 626)	DBP<90 (N=1 006 786)	DBP<100 (N=305 817)	DBP<110 (N=97 580)	DBP≥110 (N=24 885)	*P* value
Hypertension	132 705 (41.19)	343 016 (42.52)	467 395 (46.42)	177 990 (58.2)	56 632 (58.04)	14 818 (59.55)	<0.0001
Dyslipidemia	138 402 (42.96)	335 198 (41.56)	413 789 (41.1)	131 187 (42.9)	40 442 (41.44)	10 252 (41.2)	<0.0001
CKD	47 234 (14.66)	94 545 (11.72)	110 717 (11)	36 021 (11.78)	10 316 (10.57)	2494 (10.02)	<0.0001
Insulin user	39 978 (12.41)	74 080 (9.18)	75 899 (7.54)	21 702 (7.1)	5947 (6.09)	1383 (5.56)	<0.0001
Diabetes ≥5 y	127 744 (39.65)	264 586 (32.8)	284 507 (28.26)	82 214 (26.88)	21 575 (22.11)	4460 (17.92)	<0.0001
OHA≥3	56 993 (17.69)	124 848 (15.48)	136 390 (13.55)	38 481 (12.58)	10 244 (10.5)	2088 (8.39)	<0.0001
Glucose, mg/dL	140.07±47.47	143.44±46.54	145.76±46.71	147.22±46.63	150.99±48.55	155.47±51.65	<0.0001
TC, mg/dL	187.12±43.74	194.07±45.61	198.91±45.74	202.91±47.61	207.55±48.65	212.75±52	<0.0001
HDL, mg/dL	51.39±21.81	52.1±29.39	52.25±28.83	52.97±31.84	53.34±30.92	54.07±68.28	<0.0001
LDL, mg/dL	108.88±73.44	111.82±75.9	113.51±90.67	114.75±93.16	115.84±89.58	118.81±108.03	<0.0001
Creatinine, mg/dL	1.02±1.12	1.02±1.06	1.04±1.09	1.02±1.14	1.03±1.1	1.02±0.85	<0.0001
eGFR (CKD-EPI)	80.79±21.43	82.4±20.37	82.94±20.3	82.39±20.22	83.66±20.08	84.62±20.27	<0.0001

eGFR <60 mL/(min·1.73 m^2) using CKD-EPI formula. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disease, CKD-EPI, CKD Epidemiology Collaboration; DBP, diastolic BP; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; OHA, oral hypoglycemic agents; PA, physical activity; TC, total cholesterol; and WC, waist circumference.

*Alcohol consumption ≥30 g/d.

†Low income 25%.

patients (23.99% versus 20.93%) was higher in the incident ESRD group than in the non-ESRD group. SBP (134.6±18.97 versus 128.97±15.78), DBP (79.57±11.58 versus 79.05±10.27), antihypertension medication numbers and waist circumference (86.05±9.2 versus 85.43±8.89) was higher, whereas body mass index (24.68±3.51 versus 25.07±3.67) was lower in the incident ESRD group compared with the non-ESRD group. Comorbidities such as hypertension, dyslipidemia, myocardial infarction, stroke, congestive heart failure, and CKD were more prevalent in the ESRD group than in the non-ESRD group. The ESRD group showed a higher frequency of insulin use, higher frequency of patients with diabetes duration >5 years, higher number of patients taking more than 3 oral hypoglycemic agents, greater number of patients with higher fasting glucose levels but showed lower levels of high-density lipoprotein cholesterol and estimated glomerular filtration rate than that of the non-ESRD group (Table 1).

The baseline characteristics of all participants according to SBP (Table 2) and DBP (Table 3) were evaluated. The mean SBP increased with increasing age of patients, whereas patients with DBP≥110 mm Hg were the youngest. Of all participants, the number of patients with SBP <100 mm Hg, 120 mm Hg, 140 mm Hg, 160 mm Hg, and SBP≥160 mm Hg were 31 874 (1.24%), 578 750 (22.57%), 1 367 969 (23.36%), 460 020 (17.94%), and 125 257 (4.89%), respectively. The number of patients with DBP less than 70 mm Hg, 80 mm Hg, 90 mm Hg, 100 mm Hg, 110 mm Hg, and DBP≥110 mm Hg were 322 176 (12.57%), 806 626 (31.46%), 1 006 786 (39.27%), 305 817 (11.93%), 97 580 (3.81%), and 24 885 (0.97%), respectively.

Effects of Systolic BP or Diastolic BP on ESRD According to Age

The incidence rate for ESRD increased according to age and BP in both SBP and DBP categories (interaction *P* was <0.0001 for age and SBP, and 0.0022 for age and DBP). SBP<100 mm Hg was taken as the reference. In patients aged under 40 years old, the multivariable-adjusted HR (95% CI) for ESRD was 2.184 (1.207–3.950) for SBP≥160 mm Hg (Table 4, Figure [A]), whereas for DBP ≥110 mm Hg it was 4.518 (3.062–6.666; Table 5, Figure [B]). Among patients aged over 70 years old, the HR (95% CI) for SBP ≥160 mm Hg was 1.839 (1.039–3.254) and that of DBP ≥110 mm Hg was 2.338 (1.619–3.377). The composite HR for ESRD attenuated in DBP groups with increasing age (Table 5).

Subgroup Analyses

In subgroup analysis according to sex, male patients under 40 years old with SBP≥160 mm Hg showed a higher HR (HR, 3.368 [95% CI, 1.226–9.248]) compared with females (HR, 2.018 [95% CI, 0.677–6.013]) of the same age, but there was no significant difference with respect to sex among patients older than 40 years (Table S1). DBP also showed a similar pattern to SBP; compared to DBP<70 mm Hg, the HR (95% CI) for male patients under 40 years old with DBP≥110 mm Hg was 6.023 (3.826–9.484) and that of female patients was 3.168 (0.964–10.409; Table S2).

In subgroup analysis according to the use of antihypertensive medication, the nonantihypertensive medication group showed a higher HR (HR, 3.120 [95% CI, 1.506–6.466]) for ESRD compared to the antihypertensive

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Table 4. Multivariate Cox Analysis for Incident ESRD and Competing Risk of Death by SBP According to Age

Age group	SBP group	Total (n)	ESRD (n)	Duration	Incidence rate	Adjusted HR (95% CI)		Subdistribution HR (95% CI)	
						Composite	Subgroup	Composite	Subgroup
Age<40 y	<100	2300	13	15 850.22	0.82	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	<120	51 573	197	360 747.62	0.55	0.772 (0.441–1.354)	0.772 (0.441–1.354)	0.783 (0.444–1.381)	0.783 (0.444–1.382)
	<140	113 029	433	790 675.65	0.55	0.811 (0.467–1.409)	0.811 (0.467–1.409)	0.814 (0.465–1.423)	0.814 (0.466–1.423)
	<160	23 335	150	162 527.52	0.92	1.413 (0.801–2.492)	1.413 (0.801–2.492)	1.392 (0.785–2.471)	1.393 (0.785–2.472)
	≥160	6067	70	41 920.36	1.67	2.184 (1.207–3.950)	2.184 (1.207–3.950)	2.227 (1.212–4.092)	2.227 (1.212–4.092)
Age 40–49 y	<100	6593	71	45 516.75	1.56	1.268 (0.701–2.296)	1 (Ref.)	1.353 (0.739–2.474)	1 (Ref.)
	<120	122 190	653	858 351.69	0.76	0.879 (0.507–1.526)	0.693 (0.543–0.886)	0.941 (0.539–1.645)	0.696 (0.539–0.899)
	<140	254 442	1533	1 780 773.99	0.86	1.04 4 (0.603–1.806)	0.823 (0.648–1.044)	1.118 (0.642–1.949)	0.827 (0.645–1.061)
	<160	64 858	675	450 571.58	1.50	1.65 0 (0.951–2.864)	1.301 (1.018–1.663)	1.798 (1.029–3.143)	1.330 (1.029–1.717)
	≥160	16 905	307	116 077.65	2.64	2.688 (1.539–4.695)	2.119 (1.636–2.745)	3.005 (1.708–5.289)	2.222 (1.695–2.913)
Age 50–59 y	<100	10 673	122	73 207.87	1.67	1.056 (0.593–1.883)	1 (Ref.)	1.198 (0.667–2.153)	1 (Ref.)
	<120	179 787	1218	1 261 002.44	0.97	0.883 (0.508–1.534)	0.835 (0.693–1.006)	1.01 (0.577–1.767)	0.843 (0.695–1.022)
	<140	396 402	3165	2 777 845.07	1.14	1.091 (0.629–1.894)	1.033 (0.862–1.238)	1.253 (0.717–2.19)	1.046 (0.867–1.262)
	<160	121 944	1569	846 282.93	1.85	1.602 (0.922–2.786)	1.517 (1.261–1.825)	1.887 (1.079–3.301)	1.575 (1.301–1.907)
	≥160	30 481	754	209 195.08	3.60	2.569 (1.474–4.477)	2.432 (2.007–2.947)	3.220 (1.835–5.651)	2.688 (2.200–3.283)
Age 60–69 y	<100	7628	112	51 204.04	2.19	0.846 (0.470–1.522)	1 (Ref.)	1.009 (0.557–1.829)	1 (Ref.)
	<120	139 684	1286	974 361.37	1.32	0.752 (0.429–1.316)	0.889 (0.733–1.078)	0.905 (0.514–1.594)	0.897 (0.735–1.094)
	<140	358 340	4057	2 511 682.13	1.62	0.985 (0.564–1.722)	1.165 (0.965–1.406)	1.221 (0.694–2.146)	1.209 (0.997–1.467)
	<160	139 593	2354	970 900.39	2.42	1.331 (0.761–2.329)	1.574 (1.302–1.903)	1.709 (0.972–0.008)	1.694 (1.393–2.059)
	≥160	37 257	1083	257 164.68	4.21	2.023 (1.155–3.545)	2.392 (1.968–2.907)	2.668 (1.513–4.705)	2.644 (2.163–3.232)
Age≥70 y	<100	4680	64	26 656.52	2.40	0.855 (0.461–1.584)	1 (Ref.)	0.921 (0.493–1.719)	1 (Ref.)
	<120	85 516	932	532 475.75	1.75	0.885 (0.500–1.565)	1.035 (0.804–1.334)	1.033 (0.581–1.838)	1.122 (0.868–1.449)
	<140	245 756	3086	1 567 821.53	1.97	1.075 (0.609–1.897)	1.258 (0.982–1.612)	1.313 (0.740–2.33)	1.426 (1.110–1.832)
	<160	110 290	1824	700 047.99	2.61	1.357 (0.769–2.396)	1.588 (1.237–2.038)	1.694 (0.954–3.008)	1.839 (1.429–2.366)
	≥160	34 547	852	216 119.46	3.94	1.839 (1.039–3.254)	2.152 (1.669,2.775)	2.406 (1.351–4.283)	2.612 (2.019–3.378)
P for interaction									<0.0001

Adjusted for age, sex, smoking, alcohol drinking, physical activity, BMI, low income, hypertension, dyslipidemia, chronic kidney disease, diabetes duration ≥5 y, insulin user, oral hypoglycemic agents >3, estimated glomerular filtration rate, antihypertensive medication number, and type, myocardial infarction, stroke, congestive heart failure. BMI indicates body mass index; ESRD, end-stage renal disease; HR, hazard ratio; Ref, references; and SBP, systolic blood pressure.

medication group under 40 years old with SBP≥160 (HR, 1.905 [95% CI, 0.591–6.145]), but this effect was attenuated with aging (Table S3). A similar observation was observed for DBP (HR, 8.197 [95% CI, 4.648–14.456] versus HR, 1.956 [95% CI, 1.116–3.426] under 40 years old with DBP≥110), including an attenuation of

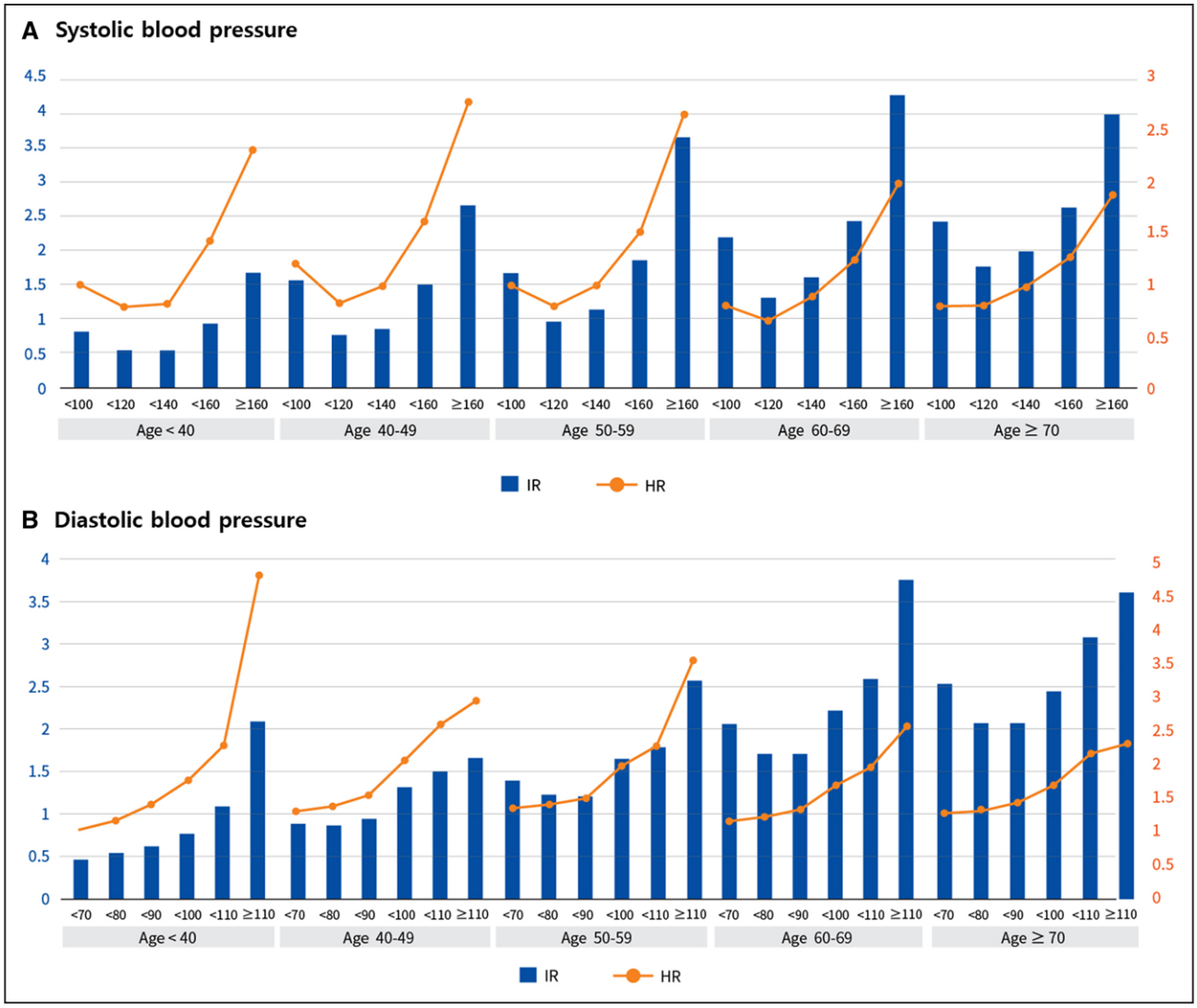

Figure. Incidence rate (IR) and hazard ratios (HR) for end-stage renal disease according to blood pressure group with age. Systolic blood pressure (**A**) and diastolic blood pressure (**B**). Adjusted for age, sex, income-low 25%, current smoker, alcohol consumption, regular exercise, hypertension, dyslipidemia, chronic kidney disease, diabetes duration ≥5 y, insulin, oral hypoglycemic agents ≥3.

the effect of DBP on ESRD development with increasing age (Table S4).

In subgroup analysis according to history of CKD, the CKD group showed a higher HR compared to the non-CKD group for SBP (Table S5) in all age groups. However, the non-CKD group showed higher HR (HR, 5.514 [95% CI, 3.494–8.703] versus HR, 4.362 [95% CI, 2.061–9.233]) for ESRD compared to the CKD group for DBP≥110 with patients under 40 years old, and effects of DBP for ESRD development was attenuated with aging in both non-CKD and CKD groups (Table S6).

DISCUSSION

The present study demonstrated that increased levels of both SBP and DBP were associated with a higher risk of ESRD. Furthermore, the younger the age, the greater the effect of hypertension on the development of ESRD was, and this effect was especially notable in men under 40 years of age, those with DBP ≥110 mm Hg, and those not taking antihypertensive drugs.

In general, diabetic nephropathy is the major cause of ESRD and hypertension contributes to further progression of kidney disease and cardiovascular disease (CVD) risk in this population.[12] ESRD is an important determinant of morbidity and mortality in patients with diabetes.[13] Hypertension is a major risk factor for CVD, which is also an important contributor to morbidity and mortality in patients with diabetes.[14] The importance of BP reduction is strengthened by previous studies which have indicated that ≈10 mm Hg decline in SBP reduced the risk of CVD by 20%, heart failure by 28%, stroke by 27%, and all-cause mortality by 13%.[15] In addition,

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Table 5. Multivariate Cox Analysis for Incident ESRD and Competing Risk of Death by Diastolic Blood Pressure According to Age

Age group	DBP group	Total (n)	ESRD (n)	Duration	Incidence rate	Adjusted HR (95% CI)		Subdistribution HR (95% CI)	
						Composite	Subgroup	Composite	Subgroup
Age<40 y	<70	19 863	65	138 127.27	0.47	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
	<80	61 673	230	431 023.80	0.53	1.163 (0.883–1.532)	1.163 (0.883–1.532)	1.144 (0.870–1.505)	1.144 (0.870–1.505)
	<90	84 639	361	592 337.87	0.61	1.430 (1.098–1.863)	1.430 (1.098–1.863)	1.388 (1.067–1.806)	1.389 (1.067–1.806)
	<100	18 673	101	130 865.54	0.77	1.776 (1.300–2.427)	1.776 (1.300–2.427)	1.730 (1.266–2.363)	1.729 (1.266–2.363)
	<110	8538	64	59 415.03	1.08	2.374 (1.680–3.354)	2.373 (1.679–3.354)	2.248 (1.578–3.201)	2.247 (1.578–3.2)
	≥110	2918	42	19 951.86	2.11	4.518 (3.062–6.666)	4.518 (3.062–6.666)	4.592 (3.071–6.867)	4.592 (3.071–6.865)
Age 40–49 y	<70	47 172	292	330 421.59	0.88	1.415 (1.077–1.859)	1 (Ref.)	1.474 (1.123–1.935)	1 (Ref.)
	<80	139 359	836	976 219.50	0.86	1.506 (1.165–1.947)	1.064 (0.931–1.216)	1.561 (1.209–2.016)	1.059 (0.926–1.212)
	<90	193 468	1288	1 355 506.04	0.95	1.670 (1.296–2.153)	1.180 (1.03901.341)	1.746 (1.357–2.248)	1.185 (1.042–1.347)
	<100	55 906	512	388 335.55	1.32	2.194 (1.687–2.853)	1.550 (1.342–1.791)	2.298 (1.769–2.986)	1.559 (1.347–1.804)
	<110	22 212	233	153 862.75	1.51	2.677 (2.025–3.540)	1.892 (1.591–2.249)	2.846 (2.156–3.758)	1.931 (1.623–2.297)
	≥110	6871	78	46 946.24	1.66	2.899 (2.078–4.045)	2.049 (1.595–2.632)	3.163 (2.266–4.416)	2.146 (1.665–2.765)
Age 50–59 y	<70	83 587	808	583 734.64	1.38	1.506 (1.154–1.966)	1 (Ref.)	1.681 (1.291–2.19)	1 (Ref.)
	<80	228 564	1956	1 601 378.01	1.22	1.594 (1.228–2.070)	1.059 (0.975–1.149)	1.784 (1.377–2.311)	1.061 (0.977–1.153)
	<90	298 004	2516	2 086 262.94	1.21	1.670 (1.288–2.166)	1.109 (1.024–1.201)	1.87 (1.445–2.42)	1.112 (1.026–1.206)
	<100	92 528	1058	643 625.62	1.64	2.184 (1.677–2.844)	1.450 (1.322–1.590)	2.486 (1.913–3.231)	1.479 (1.347–1.624)
	<110	29 559	366	204 388.39	1.79	2.415 (1.831–3.184)	1.603 (1.416–1.815)	2.76 (2.093–3.638)	1.641 (1.444–1.866)
	≥110	7045	124	48 143.78	2.58	3.530 (2.585–4.821)	2.344 (1.939–2.834)	4.306 (3.154–5.878)	2.561 (2.113–3.105)
Age 60–69 y	<70	94 412	1342	653 110.31	2.05	1.323 (1.003–1.745)	1 (Ref.)	1.584 (1.204–2.084)	1 (Ref.)
	<80	222 773	2669	1 557 219.64	1.71	1.399 (1.064–1.840)	1.058 (0.990–1.129)	1.669 (1.273–2.188)	1.054 (0.986–1.126)
	<90	256 743	3099	1 799 715.40	1.72	1.489 (1.133–1.957)	1.126 (1.055–1.200)	1.802 (1.375–2.361)	1.138 (1.066–1.214)
	<100	81 806	1264	569 884.36	2.22	1.876 (1.422–2.474)	1.418 (1.312–1.532)	2.320 (1.764–3.051)	1.465 (1.354–1.584)
	<110	22 086	398	153 446.36	2.59	2.057 (1.541–2.745)	1.555 (1.390–1.739)	2.674 (2.007–3.563)	1.688 (1.505–1.894)
	≥110	4682	120	31 936.55	3.76	2.662 (1.924–3.684)	2.012 (1.669–2.426)	3.46 (2.499–4.791)	2.184 (1.802–2.648)
Age≥70 y	<70	77 142	1217	479 644.41	2.54	1.464 (1.090–1.967)	1 (Ref.)	1.712 (1.278–2.294)	1 (Ref.)
	<80	154 257	2018	978 371.1	2.06	1.507 (1.125–2.019)	1.029 (0.958–1.105)	1.774 (1.328–2.369)	1.036 (0.963,1.114)
	<90	173 932	2274	1 108 592.06	2.05	1.583 (1.182–2.121)	1.081 (1.008–1.159)	1.883 (1.410–2.514)	1.100 (1.024,1.181)
	<100	56 904	879	360 029.31	2.44	1.825 (1.356–2.456)	1.246 (1.143–1.360)	2.210 (1.646,2.967)	1.290 (1.181–1.41)
	<110	15 185	295	95 743.77	3.08	2.256 (1.653–3.079)	1.540 (1.356–1.750)	2.792 (2.049,3.806)	1.631 (1.432–1.857)
	≥110	3369	75	20 740.61	3.62	2.338 (1.619–3.377)	1.597 (1.264–2.016)	2.953 (2.041–4.271)	1.724 (1.356–2.193)
P for interaction									0.0022

Adjusted for age, sex, smoking, alcohol drinking, physical activity, BMI, low income, hypertension, dyslipidemia, chronic kidney disease, diabetes, diabetes duration ≥5 y, insulin user, oral hypoglycemic agents >3, estimated glomerular filtration rate, antihypertensive medication number, and type, myocardial infarction, stroke, congestive heart failure. BMI indicates body mass index; ESRD, end-stage renal disease; HR, hazard ratio; Ref, references; and SBP, systolic blood pressure.

hypertension is a known independent risk factor for the development of ESRD.[16] Using a historical cohort study, Hsu et al. reported that compared with subjects with a BP less than 120/80 mm Hg, the adjusted relative risks for developing ESRD increased according to BP level and the risk for ESRD was higher in patients with diabetes compared to that in patients without.[17] A study using a large cohort of CKD showed that the risk of ESRD increased with SBP of 140 mm Hg or higher.[18] However, other studies have shown that an association exists between BP and ESRD risk at high DBP and that DBP is also known as an independent risk factor for ESRD.[19] Our study also showed that the risk for ESRD increased according to increasing SBP or DBP in all age groups, but effect of BP on ESRD weakened with age.

The presence of hypertension at a young age increases the risk of cardiovascular events in middle age.[20] Hypertension contributes to early-onset coronary heart disease, heart failure, stroke, and transient ischemic attacks.[21] Although good national guidelines exist, the guidelines do not serve low-risk young patients with hypertension as effectively as they do older patients. Furthermore, risk assessment is challenging in young patients because of the limited validity of established risk assessment tools, and a greater focus on SBP, which is less well correlated with CVD outcome.[20,22] Additionally, the causes of high SBP and DBP among young adults may differ. A higher systemic vascular resistance is a major contributor to high DBP, whereas increased aortic stiffness and a reduced aortic diameter contribute to high SBP among young adults.[23] In the current study, the highest DBP (≥110 mm Hg) group showed the highest HR compared to the highest SBP (≥160 mm Hg) group, especially in the male patient subgroup.

Although intrinsic mechanisms that regulate arterial BP are similar in men and women, marked variations exist at the molecular, cellular, and tissue levels. Previous studies have reported that compared to the BP pattern in men, women tend to show a steeper elevation in BP with age, starting from young adulthood and continuing throughout life.[24] However, women have a longer lifespan than men and develop age and CVD-related pathologies later in life; these outcomes might be due in part to sex differences in cell injury and repair pathways that delay the chronic accumulation of senescent cells, end-organ damage, and the progression of CVD.[25] In this study, the subgroup analysis for sex also showed that the ESRD risk was higher in men than in women for both SBP and DBP.

The strengths of this study include the use of a large nationwide longitudinal health screening database with high participation and outcome ascertainment rates owing to electronic linkages to universal health insurance records. This database covers a wide range of the Korean diabetes population over a long follow-up duration and, hence, allows a sizable inclusion of young adults. The events in these young participants are considered premature ESRD, an important population health outcome measure, that has rarely been studied in a large sample size to date.

However, our study also has some limitations. First, although the 2017 American College of Cardiology/American Heart Association guidelines recommend that at least 2 BP readings be obtained before determining the stage of BP, in the current study, participants were classed based on their BP readings assessed based on an average of two readings obtained during a single visit. However, in a real-world screening environment taking place on a nationwide scale, adherence to the protocol may be limited. Therefore, the BP measurements used for the classification might not have fully reflected a person's BP phenotype. Second, possible residual confounding, including sodium intake and psychological factors, may affect the association between BP and ESRD events. Third, our study was based on Korean patients with diabetes subscribing to a universal health insurance and screening program; the results should be interpreted with caution when applied to different populations or healthcare systems. Finally, longitudinal BP control or other covariates over time such as kidney function was not considered in this study.

In conclusion, among Korean patients with diabetes, those with elevated SBP or DBP were associated with a higher ESRD risk in all age groups than those with normal BP. The ESRD risk associated with BP was attenuated with age. In addition, the male patients with diabetes with high DBP and without antihypertensive medications should be screened and treated more aggressively given their particularly high risk of ESRD.

PERSPECTIVES

The incidence of ESRD is increasing according to the increasing prevalence of diabetes, and the social burden of ESRD is becoming greater. Slowing or stopping the progression to ESRD is an important public health goal. As a modifiable risk factor for ESRD, hypertension is a target that can be controlled. Our study demonstrated the enormous impact of BP on the development of ESRD, especially in young adults. Prevention of hypertension should be emphasized as a primary way to prevent ESRD, which means that a controlled study analyzing the multiple risk factors for hypertension is needed. Furthermore, early detection of persons with hypertension and treatment with antihypertensive drug therapy are essential as continuing strategies to prevent ESRD.

ARTICLE INFORMATION

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Affiliations

From the Department of Internal Medicine (E.H.B., T.R.O., S. Hyun Song, S. Heon Suh, H.S.C., C.S.K., S.K.M., S.W.K.) and Department of Pediatrics (E.M.Y.), Chonnam National University Medical School, Gwangju, Korea. Department of Internal

Medicine, Korea University Ansan Hospital (S.Y.L.). Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea (B.K., K.-D.H.).

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Disclosures

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