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Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population

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Aims There are a paucity of data on the association of duration of hypertension and blood pressure (BP) level with risk of ischaemic stroke in patients with atrial fibrillation (AF). Our objective was to investigate the association between duration of hypertension and secondly, BP levels with risk of ischaemic stroke among patients with AF.

Methods and results A total of 246 459 oral anticoagulant-naïve non-valvular AF patients were enrolled from Korea National Health Insurance Service (NHIS) database (2005–2015). The risk of ischaemic stroke according to the duration of hypertension and systolic BP (SBP) levels were assessed. One-year increase of hypertension duration continuously increased the adjusted risk of ischaemic stroke (95% confidence interval 1.07–1.09) until 7 years, and reached a plateau with adjusted hazard ratio of 1.6. Risk of ischaemic stroke increased linearly with the increase of hypertension duration in patients younger than 65 years of age, whereas the risk reached a plateau in patients aged 65 years or older. In all baseline and pre-AF average SBP subgroups, longer duration of hypertension before AF was associated with higher ischaemic stroke risk than shorter duration of hypertension (all *P*-values for trends <0.01). However, the effect of long-term hypertension was not observed in patients with strictly well-controlled pre-AF average SBP of less than 120 mmHg.

Conclusion The increase of hypertension duration was associated with the increased risk of ischaemic stroke. However, this long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension.

Keywords Atrial fibrillation • Hypertension • Ischaemic stroke • Duration • Blood pressure

Introduction

Hypertension, which is considered as the most important risk factor for stroke in the general population, is the most common comorbidity in patients with atrial fibrillation (AF) and is prevalent in approximately 80–90% of subjects with AF enrolled in recent clinical trials.[1–3] Diagnosed hypertension is an important risk factor for

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ischaemic stroke in patients with AF and is incorporated in the CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65–74, female] stroke risk stratification score, which is widely used in most guidelines for stroke prevention in AF.[4,5]

Poor blood pressure (BP) control seems to worsen outcomes in AF via left ventricular diastolic dysfunction [where associated heart failure is present, this is called 'heart failure with preserved ejection fraction (HFpEF)'], left atrial overload and remodelling.[6–10] However, most studies have reported increased risk of stroke in patients with AF who have a history of hypertension (regardless of BP level), and only few studies with relatively small sample size have reported the significance of systolic BP (SBP) level ≥140 mmHg[11] or ≥160 mmHg[12–14] in patients with AF, rather than the history of hypertension, as a risk factor for stroke in AF. Recently, our group have suggested the optimal BP target in patients with AF, which may lower the risk of ischaemic stroke as well as cardiovascular event or death.[15] However, there are a paucity of data investigating the association between duration of hypertension and risk of stroke, and it is unclear if the risk of stroke in patients with long duration of hypertension, but with well-controlled BP, have a similar risk of ischaemic stroke compared with AF patients without hypertension. Moreover, AF[4,5] and hypertension[16–18] guidelines do not have specific recommendations regarding SBP control or considering the duration of hypertension in patients with AF, particularly for stroke prevention. Therefore, a clearer understanding of the association of SBP level and duration of hypertension with the risk of stroke is needed to improve the predictive ability of the risk score among hypertensive AF patients. Our objective was to investigate the associations of duration of hypertension and BP levels with the risk of stroke in patients with AF from a nationwide cohort study.

Subjects and methods

This study is based on the national health claims database established by the National Health Insurance Service (NHIS) of Republic of Korea[19,20] and was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0179). Informed consent was waived. Further details are presented in Supplementary material online.

This study enrolled 246 459 oral anticoagulant-naïve non-valvular AF patients from NHIS database. Details are presented in *Figure 1* and Supplementary material online.

Hypertension, ischaemic stroke, and baseline comorbidities

Hypertension was defined as the combination of previous hypertension diagnosis (ICD-10 codes) and use of one or more antihypertensive drugs. Hypertension onset date for duration calculations was determined by using information on the first date of hypertension diagnosis. The comorbidities were defined at the time of AF diagnosis, and assessed annually during the follow period. The study endpoint was ischaemic stroke, which was defined with any admission diagnosis of ischaemic stroke with concomitant brain-imaging studies, including computed tomography or magnetic resonance imaging.[21] The detailed definitions of comorbidities are presented in Supplementary material online, *Table S1*.

Statistical analysis

For the duration of hypertension analysis, the duration was categorized as <3 years, 3–5 years, and ≥5 years. To assess the effect of hypertension duration and SBP levels on stroke risk, we analysed baseline SBP levels at the time of AF diagnosis in Model 1. To investigate the effect of long-term BP control on the association between hypertension duration and risk of ischaemic stroke (Model 2), we included patients who had more than two available previous health check-up data between the time of hypertension diagnosis and that of AF diagnosis, and calculated average SBP levels. Further details, including SBP analyses, are described in Supplementary material online.

Results

Baseline characteristics

Patient baseline characteristics were presented in *Table 1*. A total of 205 177 (83.2%) patients had history of diagnosed hypertension, and included in the duration analysis: 40.4% patients with duration <3 years, 15.0% with duration 3–5 years, and 44.6% with duration ≥5 years at baseline. The proportion of patients' baseline SBP level was as follows: (i) 16.8% non-hypertensive (SBP <140 mmHg); (ii) 60.4% well controlled hypertension (SBP < 140 mmHg); (iii) 17.3% uncontrolled hypertension with SBP 140–159 mmHg; and (iv) 5.5% uncontrolled hypertension with SBP ≥160 mmHg (Supplementary material online, *Table S2*).

Duration of hypertension and ischaemic stroke

In the duration of hypertension analysis, there were 533 854 person-years (mean 0.72 ± 0.41 years/patient) data included in patients with AF. Duration of hypertension and ratios for ischaemic stroke are presented in *Table 2*. When compared with non-hypertensive patients [3.33, 100 person-years (100PY)], all patients with hypertension showed higher ischaemic stroke rates regardless of duration of hypertension (100PY, 6.97 in 0–3 years, 10.82 in 3–5 years, and 13.63 in ≥5 years). In multivariable Cox models adjusted for clinical variables, hypertension duration of 0–3 years [adjusted hazard ratio (HR) 1.32, 95% confidence interval (CI) 1.24–1.42], 3–5 years (adjusted HR 1.50, 95% CI 1.38–1.64), and ≥5 years (adjusted HR 1.52, 95% CI 1.38–1.64) showed an increased adjusted risk of stroke, respectively (*Table 2*). Moreover, among hypertensive patients, compared with that of 0–3 years, hypertension duration 3–5 year and ≥5 years increased the risk of ischaemic stroke with adjusted HRs of 1.31 (95% CI 1.25–1.38) and 1.40 (95% CI 1.34–1.47), respectively.

Figure 2 demonstrates the adjusted HRs associated with duration of hypertension modelled as continuous variable using a cubic spline for the ischaemic stroke. These analyses confirm an approximately linear dose–response relationship between the duration of hypertension and the risk of ischaemic stroke. One-year increase in duration of hypertension continuously increased the adjusted risk of ischaemic stroke until 7 years of hypertension (adjusted HR 1.08, 95% CI 1.07–1.09), and reached a plateau with

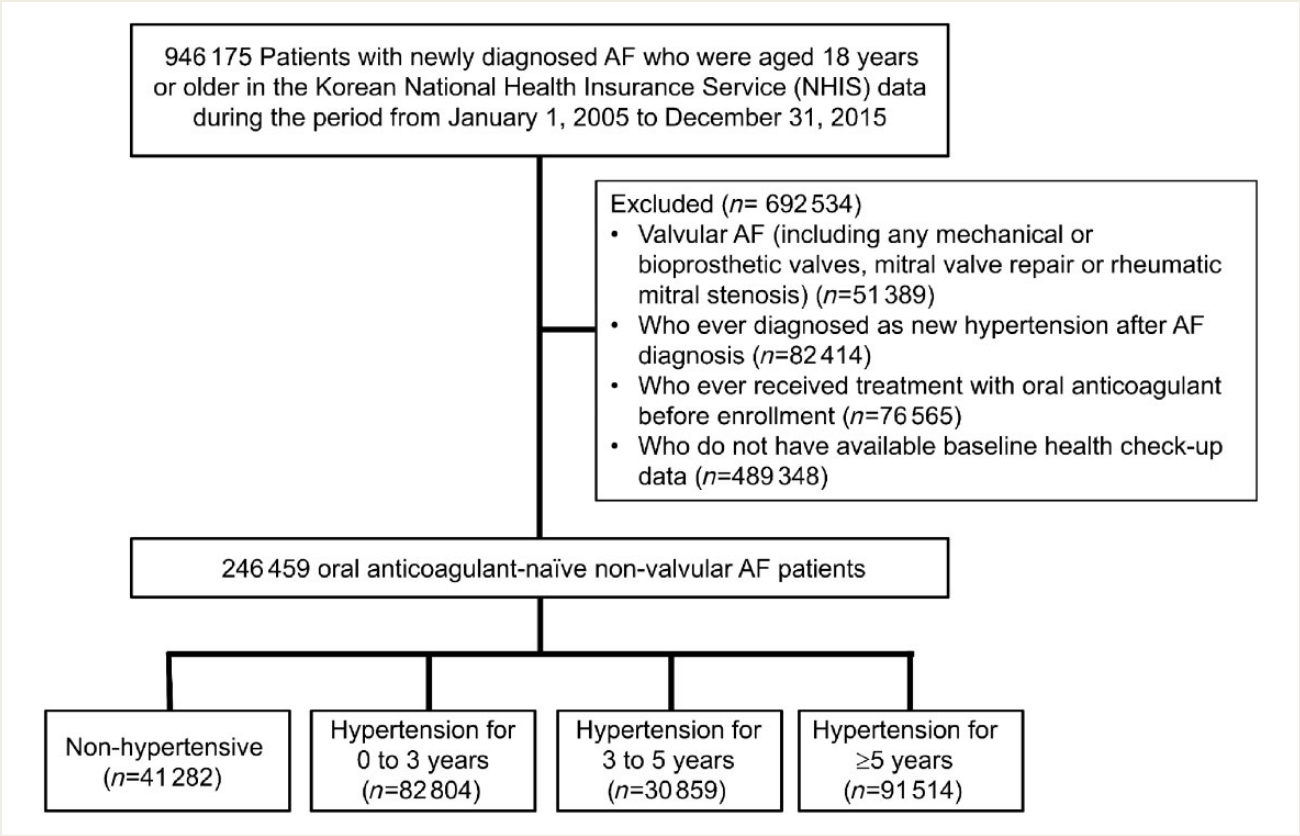


Figure 1 Flowchart of study population enrolment and analyses.

adjusted HR of 1.6 (adjusted HR 1.00, 95% CI 0.09–1.02 after 7 years of hypertension duration).

When stratified by age subgroups, the risk of ischaemic stroke continuously increased linearly with the increase of hypertension duration in subgroups of ages ≤55 and 55 to 64-years, and then reached plateau in subgroup aged 65–74 years and in those aged ≥75 years (*Figure 3*). Similar trends were observed in the competing-risk regression analyses for the all-cause mortality (Supplementary material online, *Table S4*, *Figure S5*).

Duration of hypertension in different disease subgroups and sensitivity analyses

Table 3 shows subgroup analyses and sensitivity analyses for the adjusted HRs of 1-year ischaemic stroke associated with duration of hypertension. In subgroup analyses, longer duration of hypertension increased the risk of ischaemic stroke regardless of heart failure, diabetes mellitus, prior stroke/transient ischaemic attack (TIA), and chronic kidney disease. Particularly, the effect of hypertension duration on stroke risk was greater for the patients with heart failure, when compared with those without ($P < 0.01$ for interaction). In sensitivity analyses, longer duration of hypertension increased the risk of ischaemic stroke under the following conditions: after excluding patients with prior stroke/TIA history; after excluding patients with baseline comorbidities such as heart failure, diabetes, vascular disease, and chronic kidney disease; after excluding patients with intracranial haemorrhage occurred during follow-up period; or after including systemic embolic event as an outcome.

Duration of hypertension in different systolic blood pressure levels

Kaplan–Meier analysis for crude rate of ischaemic stroke according to baseline SBP levels (at the time of AF diagnosis) showed that patients with lower SBP <120 mmHg at baseline had higher cumulative survival free of ischaemic stroke than other SBP levels (log rank $P < 0.001$) (Supplementary material online, *Figure S1*). A 10-mmHg increase in SBP level increased the adjusted risk of stroke (adjusted HR 1.06, 95% CI 1.05–1.07) (Supplementary material online, *Figure S2*).

Figure 4 shows the risk for ischaemic stroke according to the duration of hypertension in patients with different baseline SBP categories (Model 1). In all subgroups with different baseline SBP levels, significantly increasing trends in stroke risk were observed with increasing duration of hypertension among hypertensive patients (all *P*-values for trends <0.01). Moreover, the presence of hypertension (regardless of duration) was associated with higher risk of ischaemic stroke compared with non-hypertensive patients (2.97 per 100PY). Hypertensive patients with duration ≥5 years and baseline SBP ≥160 mmHg showed adjusted HR of 2.25 for ischaemic stroke (95% CI 1.94–2.60, 19.16 per 100PY), whereas those with duration <3 years and baseline SBP <120 mmHg showed adjusted HR of 1.36 (95% CI 1.22–1.52, 6.38 per 100PY).

Table 1 Patient characteristics by estimated hypertension duration at baseline

	Non-hypertensive (*n* = 41 282)	Hypertension				
		0–3 years (*n* = 82 804)	3–5 years (*n* = 30 859)	≥5 years (*n* = 91 514)	SMD[a]	SMD[b]
Age (years)	51 ± 14	61 ± 12	64 ± 11	68 ± 10	1.092	0.513
<65	33 871 (82.0)	46 630 (56.3)	14 431 (46.8)	31 265 (34.2)		
65–74	5453 (13.3)	25 557 (30.9)	5330 (35.9)	23 938 (39.6)		
>75	1958 (4.7)	10 617 (12.8)	5330 (17.3)	23 938 (26.2)		
Women	16 738 (40.5)	31 260 (37.8)	13 196 (42.8)	41 831 (45.7)	0.031	0.134
CHA_2DS_2-VASc score	0.8 ± 1.0	2.5 ± 1.6	3.2 ± 1.6	3.8 ± 1.8	1.636	0.622
TIA/ischaemic stroke history	1858 (4.5)	11 446 (13.8)	6165 (20.0)	25 785 (28.2)	0.514	0.311
Vascular disease	1269 (3.1)	10 234 (12.4)	4900 (15.9)	21 934 (24.0)	0.503	0.276
Previous MI	510 (1.2)	6034 (7.3)	2266 (7.3)	8724 (9.5)	0.336	0.080
PAD	780 (1.9)	5006 (6.0)	3043 (9.9)	15 476 (16.9)	0.391	0.306
Heart failure	963 (2.3)	19 082 (23.0)	7632 (24.7)	28 052 (30.7)	0.737	0.161
Diabetes	2149 (5.2)	12 400 (15.0)	6406 (20.8)	25 627 (28.0)	0.497	0.278
ESRD	1 (0.0)	5 (0.0)	8 (0.0)	147 (0.2)	0.038	0.051
CKD	363 (0.9)	1756 (2.1)	1067 (3.5)	5965 (6.5)	0.216	0.196
Dyslipidaemia	13 254 (32.1)	40 946 (49.4)	19 325 (62.6)	71 811 (78.5)	0.682	0.557
Household income					0.034	0.176
Upper 20%	10 558 (25.6)	18 866 (22.8)	7312 (23.7)	26 820 (29.3)		
Middle 40%	16 195 (39.2)	29 133 (35.2)	11 125 (36.1)	33 419 (36.5)		
Lower 40%	14 529 (35.2)	34 805 (42.0)	12 422 (40.3)	31 275 (34.2)		
SBP (mmHg)	121.72 ± 15.67	129.03 ± 17.89	130.70 ± 17.43	130.47 ± 16.74	0.869	0.057
DBP (mmHg)	75.86 ± 10.33	79.69 ± 11.59	80.06 ± 11.28	79.09 ± 10.90	0.593	0.063
Smoking					0.185	0.095
Current	9558 (23.4)	15 299 (18.80)	4647 (15.3)	11 325 (12.4)		
Former	6942 (17.0)	13 522 (16.6)	4975 (16.4)	18 535 (20.4)		
BMI	23.2 ± 3.0	24.2 ± 3.3	24.5 ± 3.3	24.7 ± 3.4	0.408	0.131
≥25	13 323 (32.3)	37 909 (45.8)	15 270 (49.5)	47 709 (52.1)	0.349	0.107
≥30	1044 (2.5)	4412 (5.3)	2067 (6.7)	7315 (8.0)	0.201	0.091
LDL cholesterol	113.5 ± 34.0	110.2 ± 36.1	108.4 ± 36.2	105.3 ± 35.7	0.130	0.080
eGFR	88.2 ± 19.8	81.0 ± 19.8	77.7 ± 19.8	72.4 ± 20.7	0.653	0.374
Medication						
Antiplatelet agent	1799 (4.4)	28 130 (34.0)	14 567 (47.2)	58 292 (63.7)	1.175	0.542
Statin	2688 (6.5)	12 753 (15.4)	7855 (25.5)	38 237 (41.8)	0.609	0.534
Beta-blocker	1778 (4.3)	20 096 (24.3)	11 835 (38.4)	49 520 (54.1)	0.945	0.548
RAS blockade	82 (0.2)	22 186 (26.8)	13 780 (44.7)	57 460 (62.8)	1.282	0.657
Calcium-channel blocker	93 (0.2)	17 394 (21.0)	14 436 (46.8)	60 588 (66.2)	1.268	0.828
Loop/thiazide diuretics	733 (1.8)	22 259 (26.9)	13 899 (45.0)	57 403 (62.7)	1.203	0.651
K+ sparing diuretics	271 (0.7)	5071 (6.1)	2062 (6.7)	8215 (9.0)	0.351	0.102

Values are expressed in *n* (%) or mean ± standard deviation.
Vascular disease includes previous myocardial infarction, PAD, or aortic plaque.
BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; Duration of hypertension, duration of hypertension at the time of AF diagnosis; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); ESRD, end-stage renal disease; HTN, hypertension; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral arterial disease; RAS, renin–angiotensin system; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Standardized difference between non-hypertensive vs. hypertension.
[b]Standardized difference between hypertension with duration ≥5 years vs. hypertension with duration <5 years.

Improvement in the predictive ability of modified CHA_2DS_2-VASc, which was calculated using hypertension with duration ≥5 years and SBP ≥160 mmHg as two points, was compared with CHA_2DS_2-VASc score, and the area under ROC curve (AUC) of the modified CHA_2DS_2-VASc scoring system was improved from 0.647 to 0.648 ($P < 0.001$). These improvements in the predictive ability of risk scoring schemes were also observed in the $CHADS_2$ and the ATRIA score (Supplementary material online, *Table S3*).

Table 2 Duration of hypertension and hazard ratios for 1-year ischaemic stroke

	Non-hypertensive	Hypertension Duration at AF diagnosis		
		0–3 years	3–5 years	≥5 years
Ischaemic stroke events (1-year outcome)	1215	4887	2619	9033
Person-years	36 462	70 099	24 204	66 275
Stroke rate, 100 person-years (95% CI)	3.33 (3.15–3.53)	6.97 (6.78–7.17)	10.82 (10.41–11.24)	13.63 (13.35–13.91)
Among all patients				
HR (unadjusted) (95% CI)	Ref	2.04 (1.91–2.17)	2.98 (2.78–3.19)	3.40 (3.18–3.63)
HR (adjusted[a]) (95% CI)	Ref	1.32 (1.24–1.42)	1.50 (1.38–1.64)	1.52 (1.39–1.65)
HR (age-stratified[b]) (95% CI)	Ref	1.32 (1.23–1.41)	1.50 (1.38–1.63)	1.51 (1.39–1.65)
Among hypertensive patients				
HR (unadjusted) (95% CI)	NA	Ref	1.48 (1.41–1.55)	1.76 (1.70–1.82)
HR (adjusted[a]) (95% CI)	NA	Ref	1.31 (1.25–1.38)	1.40 (1.35–1.46)
HR (age-stratified[b]) (95% CI)	NA	Ref	1.33 (1.26–1.39)	1.41 (1.36–1.47)
HR (unadjusted) (95% CI)	NA	NA	Ref	1.19 (1.14–1.25)
HR (adjusted[a]) (95% CI)	NA	NA	Ref	1.07 (1.03–1.12)
HR (age-stratified[b]) (95% CI)	NA	NA	Ref	1.06 (1.01–1.10)

CI: confidence interval; Duration of hypertension, duration of hypertension at the time of AF diagnosis; HR, hazard ratio; NA, not available; Ref, reference.
[a]Adjusted for CHA_2DS_2-VASc components [congestive heart failure, hypertension, age (continuous covariate), previous stroke, vascular disease, and sex], dyslipidaemia, chronic kidney disease, body mass index, smoking status, income status, and systolic blood pressure level.
[b]Adjusted for CHA_2DS_2-VASc components [congestive heart failure, hypertension, age (continuous covariate), previous stroke, vascular disease, and sex], dyslipidaemia, chronic kidney disease, body mass index, smoking status, income status, and systolic blood pressure level + additionally adjusted for age deciles (stratified cox proportional hazards model).

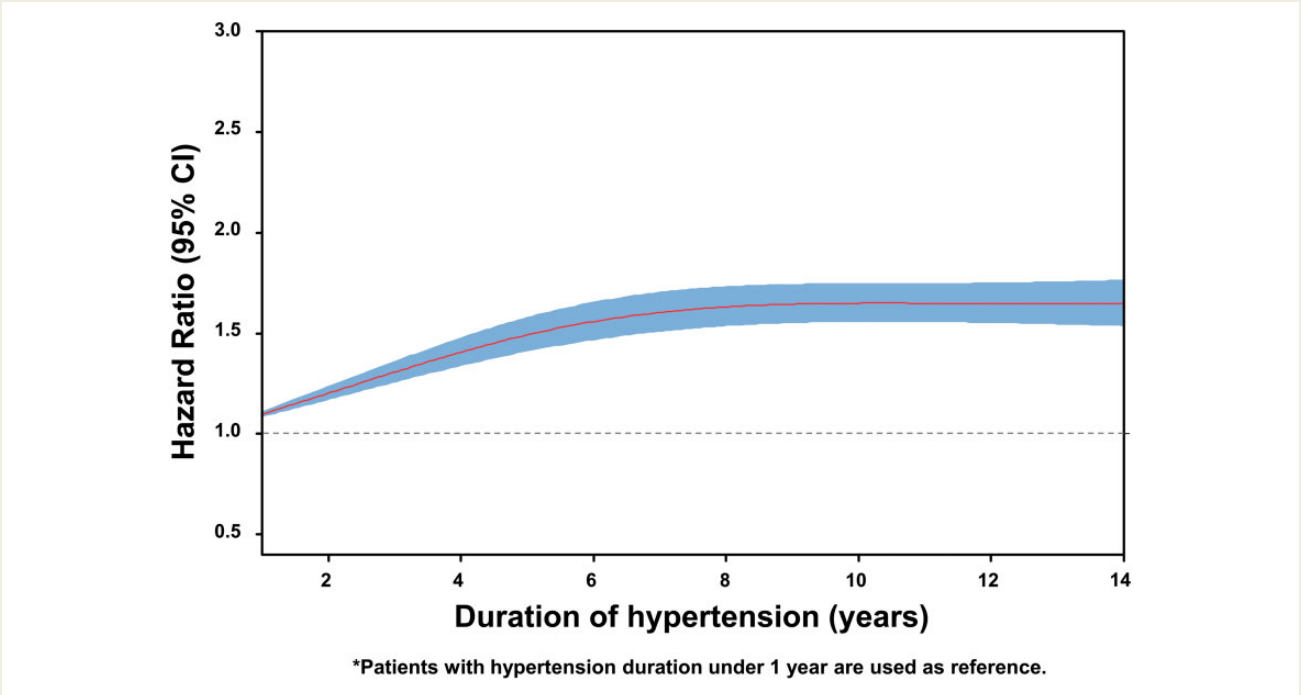


Figure 2 Duration of hypertension at the time of atrial fibrillation diagnosis and adjusted hazard ratios for ischaemic stroke in patients with atrial fibrillation. Curves represent hazard ratios adjusted for CHA_2DS_2-VASc components, dyslipidaemia, chronic kidney disease, smoking status, body mass index, income status, and systolic blood pressure level. Solid red lines are the best-fitted linear models, and blue colour areas are 95% confidence intervals for the spline curves. Patients with hypertension duration under 1 year are used as reference.

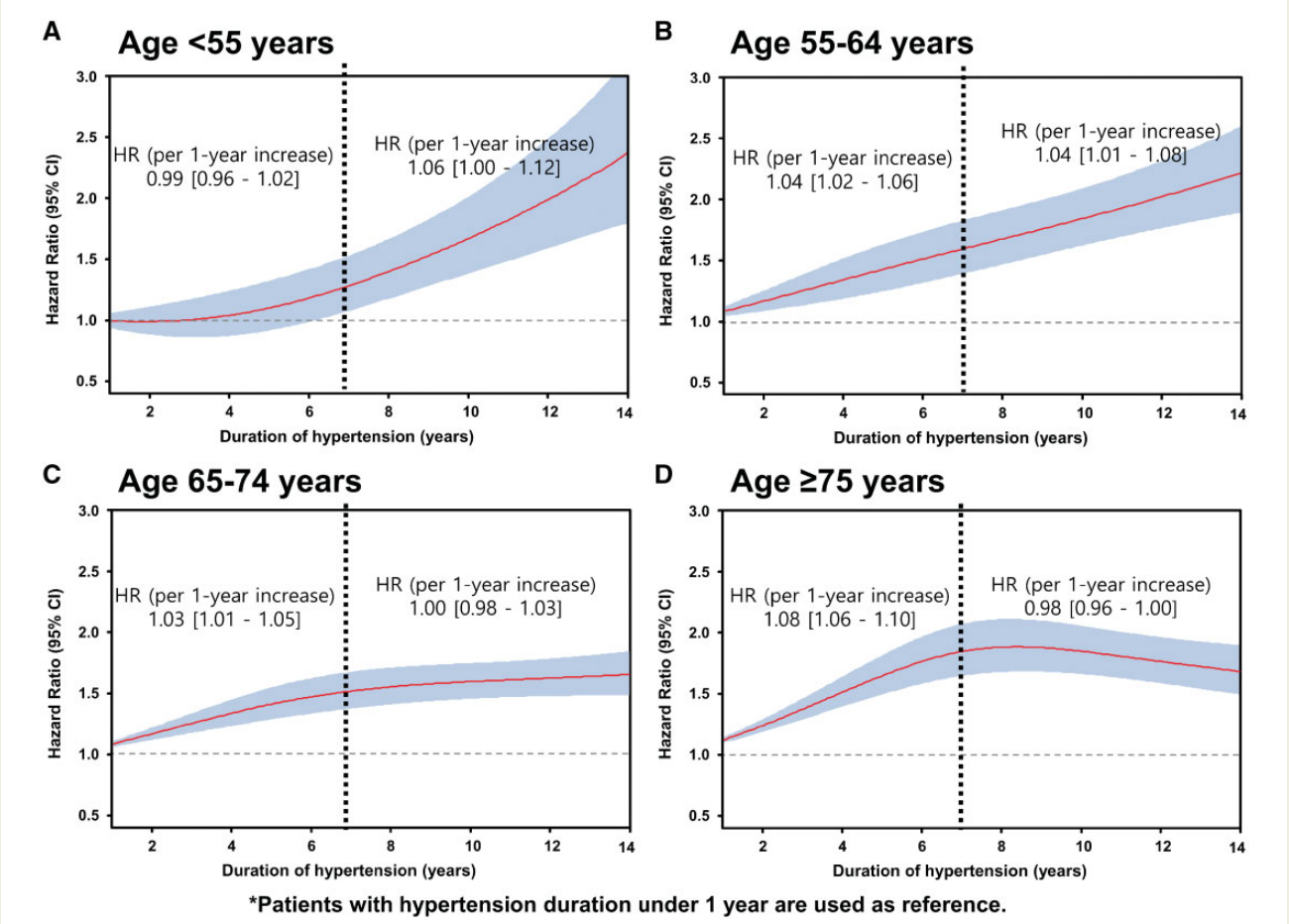


Figure 3 Duration of hypertension at the time of atrial fibrillation diagnosis and adjusted hazard ratios for 1-year ischaemic stroke in atrial fibrillation patients with different age categories. (*A*) Age <55 years. (*B*) Age 55–64 years. (*C*) Age 65–74 years. (*D*) Age ≥75 years. Patients with hypertension duration under 1 year are used as reference.

Average systolic blood pressure control levels before atrial fibrillation diagnosis

Of the overall study population, 78.8% patients (194 108 out of 246 459) had at least two BP measurements before diagnosis of AF (between diagnosis of hypertension and AF), and average SBP values were used in the analyses (Model 2, *Take home figure*). Results were similar with those using baseline SBP levels (Model 1), and hypertensive patients with duration ≥5 years and pre-AF average SBP ≥160 mmHg showed adjusted HR of 1.95 for ischaemic stroke (95% CI 1.56–2.44, 20.44 per 100PY) when compared with non-hypertensive patients (3.17 per 100PY). However, in patients with pre-AF average of SBP <120 mmHg, patients with all hypertension duration categories showed no significant differences in adjusted HRs for ischaemic stroke [1.11 (0.97–1.28) for 0–3 years, 1.03 (0.84–1.26) for 3–5 years, and 1.18 (1.00–1.39) for ≥5 years] when compared with non-hypertensive patients.

Change in the total number of anti-hypertensive medication and risk of stroke

The risk of stroke according to the change in total number of BP medications (before the AF diagnosis date) was assessed. Total number of BP medications was reduced, not changed, and increased during the period from the hypertension diagnosis date to the AF diagnosis date in 31 320 (12.7%), 128 059 (51.9%), and 87 151 (35.4%) patients, respectively. Linear dose–response relationship between the duration of hypertension and the risk of ischaemic stroke according to changes in the number of BP medication are presented in Supplementary material online, *Figure S3*. The risk of stroke was increased in patients with stopped, reduced, or no-changed number of BP medication (probably in relation to insufficient BP control and non-adherence/non-persistence). In contrast, the effect of hypertension duration on the risk of stroke was relatively lower in patients with increased number of BP medications (which could mean

Table 3 Subgroup analyses and sensitivity analyses of the adjusted hazard ratios of 1-year ischaemic stroke associated with duration of hypertension

	Adjusted hazard ratio (95% CI) (per 1-year increase)	
Total population	1.05 (1.04–1.06)	
Subgroup analyses		*P*-value for interaction
Heart failure		
Yes	1.12 (1.10–1.15)	<0.001
No	1.02 (1.01–1.03)	
Diabetes mellitus		
Yes	1.06 (1.04–1.08)	0.903
No	1.04 (1.03–1.05)	
Prior stroke/TIA		
Yes	1.04 (1.02–1.06)	0.294
No	1.05 (1.03–1.06)	
Chronic kidney disease		
Yes	1.05 (1.00–1.12)	0.379
No	1.04 (1.03–1.05)	
Sensitivity analyses		
Excluded patients with prior stroke/TIA history	1.06 (1.05–1.06)	
Excluded patients with baseline comorbidities such as heart failure, diabetes, vascular disease, and chronic kidney disease	1.06 (1.05–1.06)	
Excluded patients with intracranial haemorrhage occurred during follow-up period	1.03 (1.02–1.03)	
Included systemic embolic event as an outcome	1.03 (1.02–1.03)	

Duration of hypertension, duration of hypertension at the time of AF diagnosis; TIA, transient ischaemic attack.

aggressive adjustment of BP medication). Patients with increased numbers of BP medications had a lower risk of ischaemic stroke than other patients.

Discussion

In this analysis of >240 000 oral anticoagulant naïve AF patients in the entire Korean population, there are three major findings. First, 1-year increase of hypertension duration continuously increased the adjusted risk of ischaemic stroke (adjusted HR 1.08, 95% CI 1.07–1.09) until 7 years, and reached a plateau with adjusted HR of 1.6 (adjusted HR 1.00, 95% CI 0.98–1.02 after 7 years of hypertension duration). The risk of ischaemic stroke increased linearly with the increase of hypertension duration in patients younger than 65 years, whereas the risk reached plateau in patients aged 65 years or older. Second, in all baseline SBP groups, including those with well-controlled SBP (SBP <120 mmHg or 120–139 mmHg), longer duration (≥3 years) of hypertension was associated with higher risk of ischaemic stroke compared with shorter duration (<3 years). Finally, in patients with strictly controlled SBP (pre-AF average SBP less than 120 mmHg), hypertension (even with long duration) was not associated with higher ischaemic stroke risk when compared with non-hypertensive patients. Our study suggests that an increased duration of hypertension was associated with an increased risk of ischaemic stroke even in patients with well controlled SBP level at the time of AF diagnosis and initial stroke risk stratification. However, the increased risk of ischaemic stroke seen with long-term hypertension can be attenuated by continuously applied strict BP control before AF diagnosis.

Duration of hypertension and the risk of ischaemic stroke

Patients with hypertension were at higher risk of ischaemic stroke events compared with patients without hypertension, and importantly, the longer duration of hypertension had higher risk of ischaemic stroke than shorter duration. On the other hand, several studies have reported that in diabetes, which is an important risk factor for ischaemic stroke in AF, the longer estimated duration of the disease was strongly associated with an increase in adjusted rate of ischaemic stroke.[22,23] Ashburner *et al.*[22] have shown that duration of diabetes is a more important predictor of ischaemic stroke than glycaemic control in patients who have diabetes and AF, suggesting the different mechanisms of ischaemic stroke between AF and non-AF patients.

The mechanisms linking hypertension duration to an increased stroke risk are multifactorial. Long-standing hypertension, particularly if sub-optimally controlled, could lead to left ventricular hypertrophy, left atrial enlargement/fibrosis, and diastolic dysfunction, all of which may contribute to the increased burden of AF and consequently increased risk of ischaemic stroke,[6–10] as well as non-cardioembolic stroke.[24]

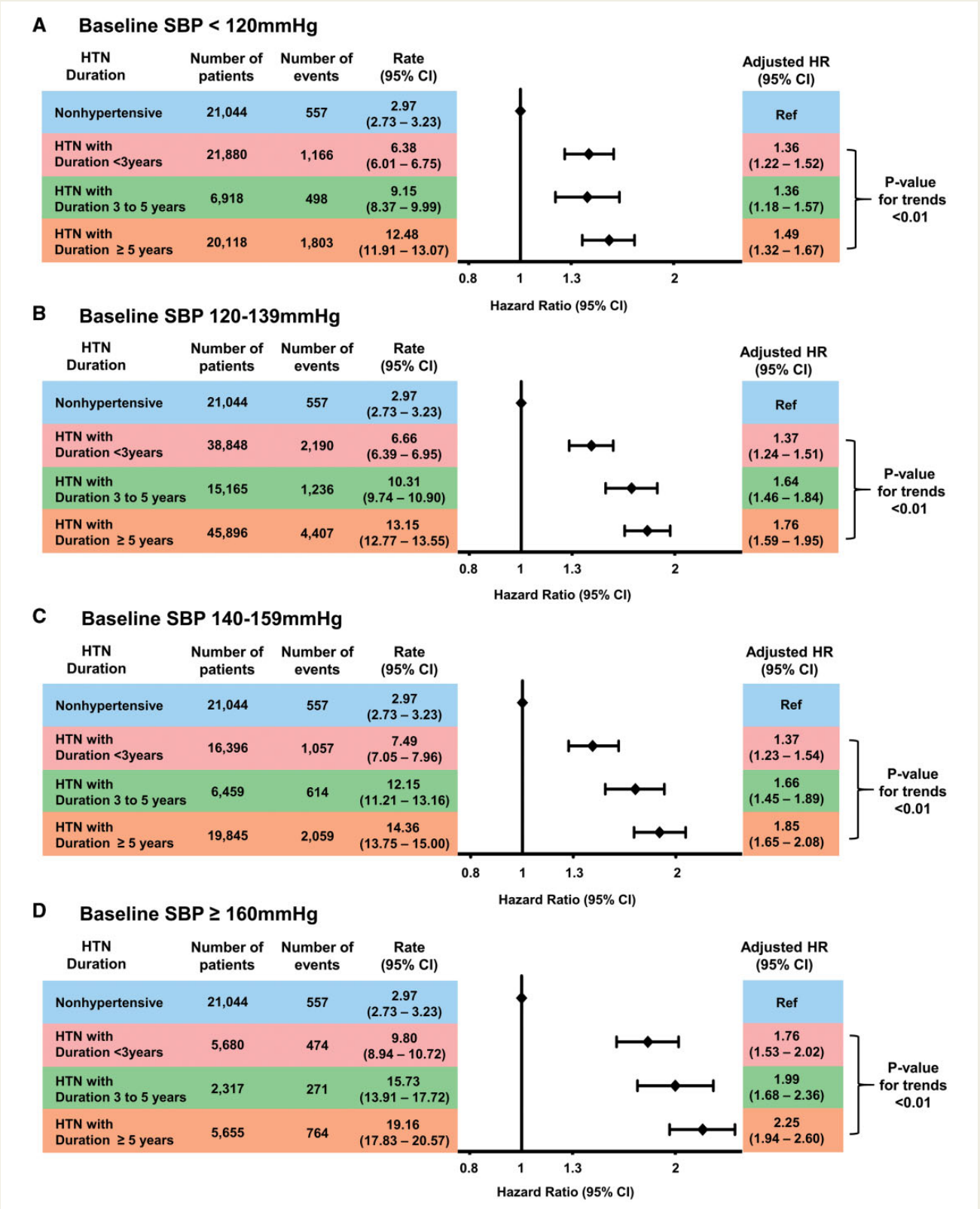
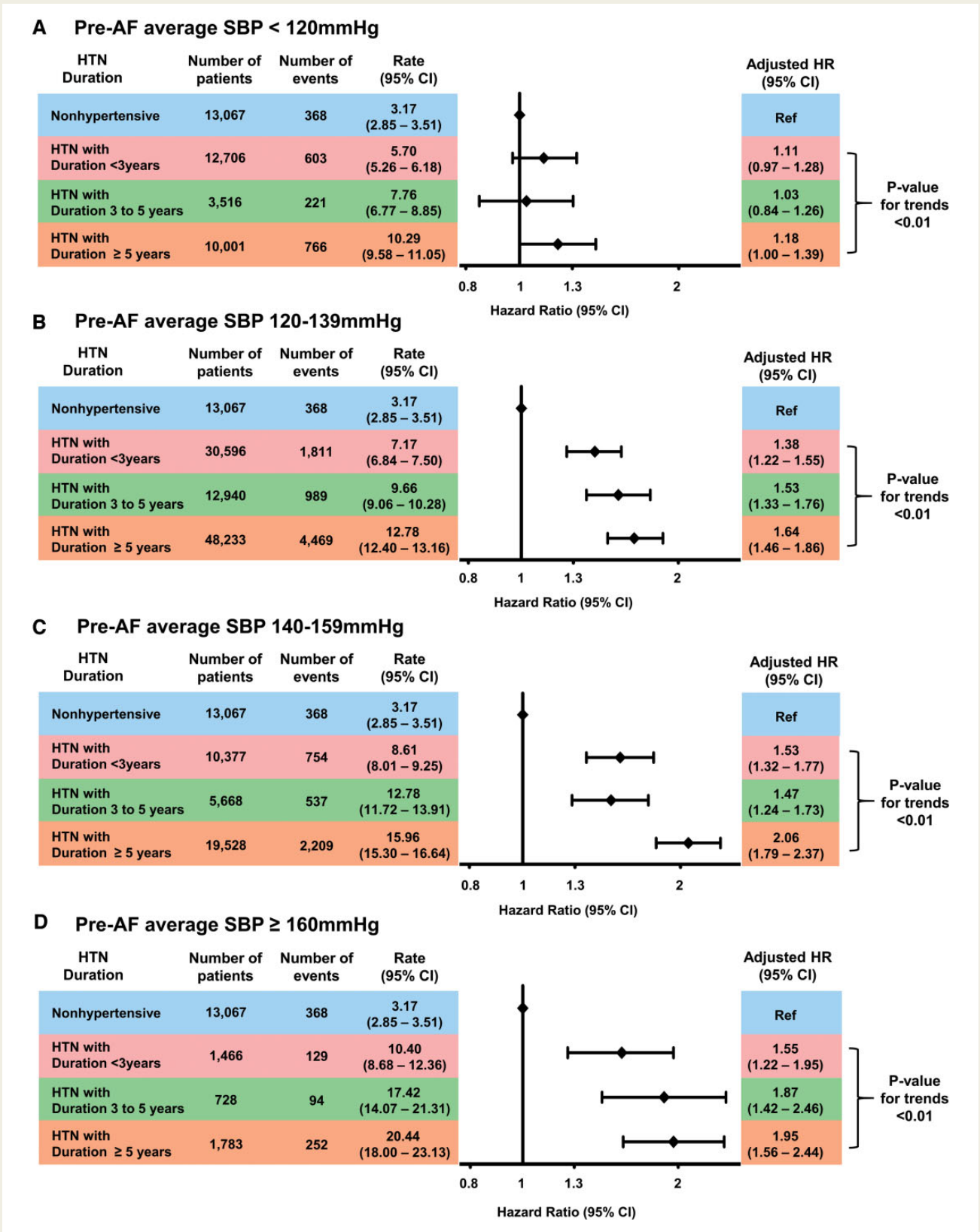


Figure 4 Risk of ischaemic stroke according to duration of hypertension in patients with different baseline systolic blood pressure subgroups. (*A*) Baseline systolic blood pressure <120 mmHg. (*B*) Baseline systolic blood pressure 120–139 mmHg. (*C*) Baseline systolic blood pressure 140–159 mmHg. (*D*) Baseline systolic blood pressure ≥160 mmHg. Duration of hypertension, duration of hypertension at the time of atrial fibrillation diagnosis.



Take home figure Risk of ischaemic stroke according to duration of hypertension in patients with atrial fibrillation in different pre-atrial fibrillation average systolic blood pressure subgroups. (*A*) Baseline systolic blood pressure <120 mmHg. (*B*) Baseline systolic blood pressure 120–139 mmHg. (*C*) Baseline systolic blood pressure 140–159 mmHg. (*D*) Baseline systolic blood pressure ≥160 mmHg. Duration of hypertension, duration of hypertension at the time of atrial fibrillation diagnosis.

In this study, the risk of ischaemic stroke after AF diagnosis increased linearly with the increase of SBP. However, interestingly, hypertension duration showed a linear dose–response relationship with plateau in patients except for those who were younger than 65 years old. This result has important clinical implication, as it suggests that in younger patients, longer duration of hypertension can increase the risk of stroke continuously if it is not strictly controlled.

Effect of hypertension duration according to systolic blood pressure levels

The longer duration of hypertension was associated with higher ischaemic stroke risk, even in patients with well-controlled baseline SBP (SBP <120 mmHg or 120–139 mmHg) level at the time of AF diagnosis. This result suggests that, even if patients with first diagnosed AF have well controlled baseline SBP level and do not have no other risk factors for ischaemic stroke, potential risk of stroke should not be overlooked in the initial stroke risk stratification if they have long duration of hypertension history. Although the CHA_2DS_2-VASc stroke risk score used in most AF guidelines includes a diagnosis of hypertension as a stroke risk factor,[4,5] there is no specific definition on the duration of hypertension and stroke risk, given the lack or prior data regarding the association between hypertension duration and risk of ischaemic stroke in AF, as well as cardiovascular risk. By including longer duration and higher SBP in modified CHA_2DS_2-VASc stroke, the predictive values of CHA_2DS_2-VASc score for ischaemic stroke could be improved, particularly in hypertensive patients. It has important clinical implications, given that it is unclear (with different recommendations among international guidelines) whether oral anticoagulant should be prescribed in young AF patient with no risk factor other than hypertension (therefore would be categorized as intermediate risk with CHA_2DS_2-VASc score one in males and two in females).

Strict blood pressure control and the risk of stroke

The 2017 AHA/ACC guidelines recently lowered the recommended threshold for the diagnosis of hypertension from ≥140/90 mmHg to ≥130/80 mmHg in the general population.[18] However, all published guidelines do not have specific recommendations for BP targets in patients with AF, especially for stroke prevention. Although longer duration of hypertension was associated with higher ischaemic stroke risk, hypertension (even with long duration) was not associated with higher ischaemic stroke risk in patients with strict SBP control who had pre-AF average SBP <120 mmHg, compared with non-hypertensive patients. These results strongly suggest that the long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension. Moreover, in SBP analysis of current data set (Supplementary material online, *Figures S1* and *S4*), baseline SBP <120 mmHg group showed significant benefit compared with baseline SBP 120–139 mmHg group. The result of this study suggests that AF patients with longer hypertension duration and/or uncontrolled SBP levels should be categorized as 'high risk', and that strict BP control over the entire duration of hypertension, combined with oral anticoagulant, would be very important for reducing the risk of ischaemic stroke.

Limitations

The present study has several limitations. Although administrative databases are increasingly used for clinical research, such studies are potentially susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that we already validated in previous studies that used a Korean NHIS sample cohort.[21,25–28] Because data regarding types of AF (paroxysmal vs. non-paroxysmal) were not available, we could therefore not investigate whether the effect of hypertension duration and/or SBP level differed according to types of AF. Since health examinations supported by the National Health Insurance System were performed in different hospitals and clinics, there was a lack of uniformity of BP measuring devices. Because this database study evaluated only the first-year ischaemic stroke outcome after AF diagnosis, further evidence is required to establish the association between the duration of hypertension and long-term risk of ischaemic stroke after AF diagnosis. Finally, there was no available information about ambulatory BP monitoring data. Therefore, analyses of BP levels using this health examination data should be interpreted with caution; however, to overcome this, this study also analysed 194 108 (78.8%) patients with at least two BP measurement before AF diagnosis. Despite these limitations, this study included the evaluation of longitudinal data from the *entire* Korean adult population. Therefore, our findings reflect the ischaemic stroke risk of 'real world' AF regarding the effect of hypertension duration and SBP levels on ischaemic stroke in oral anticoagulant naïve AF on nationwide scale.

Conclusions

The longer duration of hypertension before AF diagnosis was associated higher risk of ischaemic stroke regardless of SBP levels at AF diagnosis. This long-term effect of hypertension duration can be attenuated by long-term strict SBP control throughout the entire duration of hypertension. The result of this study suggests that AF patients with longer hypertension duration, as well as uncontrolled SBP levels, should be categorized as 'high risk' and strict BP control with oral anticoagulant would be important to reduce the risk of ischaemic stroke.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: G.Y.H.L.: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees were received personally. J.B.Y.: Research fund from Abbort. All other authors declared no conflict of interest.

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