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COMMENT

Is atrial fibrillation a suitable target for studies on blood pressure variability?

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Several blood pressure (BP) variability indices, including intraday fluctuations, beat-to-beat, day-to-day, visit-to-visit variability (VVV), and seasonal variations, have been found to be associated with the incidence of adverse events. In particular, BP-VVV, an index of long-term BP variability [1], is reportedly a risk factor for various cardiovascular events and mortality in patients with hypertension, as well as the general population [2–6]. Although atrial fibrillation (AF) and hypertension often coexist in the same patient [7], the influence of BP variability on adverse events in patients with AF has not been sufficiently elucidated [8, 9]. One reason for this may be that patients with AF were often excluded or not considered in previous large-scale clinical trials on hypertension [2, 10], as AF is an absolute arrhythmia; thus, beat-to-beat BP variability is originally large due to irregular heartbeats. In general, accurate sphygmomanometry is often difficult in patients with AF, but proportionate values of BP can be obtained using the cuff-oscillometric method unless patients have bradycardia [11]. When three repeated measurements were performed, the AF did not significantly affect the accuracy of the oscillometric BP measurements [12]. Therefore, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) recommend performing repeated BP measurements three or more times and adopting the average in further consideration [7].

Thus far, relatively few studies have investigated the association between BP-VVV and clinical outcomes in patients with AF. First, Proietti et al. [8] reported their association in a post hoc analysis of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study in 2017 [8], in which the standard deviation (SD) of systolic BP during the follow-up period was adopted as an index of BP-VVV and BP was measured using standard procedures, while no specific procedures were recommended from the study protocol. In this study, the third and fourth (highest) quartiles of systolic BP-SD were independently associated with higher risks for stroke (adjusted hazard ratio [HR] 1.85, 95% confidence interval [CI] 1.02–3.35 and HR 2.33, 95% CI 1.30–4.16, respectively) and major hemorrhage (HR 1.92, 95% CI 1.18–3.15 and HR 2.88, 95% CI 1.79–4.61, respectively) compared with the first (lowest) quartile. Patients in the highest quartile also had an increased risk of all-cause mortality (HR 1.38, 95% CI 1.00–1.91) [8]. Second, Kodani et al. reported an association between BP-VVV and adverse events in patients with non-valvular AF in a subanalysis of the J-RHYTHM Registry in 2021 [9], in which the SD and coefficient of variation (CV) of systolic BP were evaluated as indices of BP-VVV, while BP values were obtained using the auscultatory method or an automated sphygmomanometer, as appropriate, during daily clinical practice in each institution. In this study, the highest quartile of systolic BP-SD was significantly associated with increased risks of thromboembolism (HR 2.00, 95% CI 1.15–3.49), major hemorrhage (HR 2.60, 95% CI 1.36–4.97), and all-cause death (HR 1.85, 95% CI 1.11–3.07), even after adjusting for multiple confounding factors [9]. This was also true when BP-CV was used instead of BP-SD [9]. Furthermore, systolic BP-SD was found to be superior to several other BP indices, such as systolic BP at baseline and at the time closest to an event or at the last follow-up visit [9], time in target range, and frequency in range, as a predictor of adverse events [13].

In the current issue of *Hypertension Research*, Chicharoen et al. [14] described the association between BP-VVV and clinical outcomes in Asian patients with AF who

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underwent BP measurements at least three times (baseline and at least two other visits) in the COOL-AF Registry, in which systolic BP-SD was used as an index of BP-VVV, and three repeated BP measurements at each visit were encouraged [12]. The results of this study [14] were similar to those of previous post hoc analyses of the AFFIRM Study [8] and the J-RHYTHM Registry [9]. That is, patients in the highest quartile of systolic BP-SD had significantly higher risks for major bleeding (HR 1.92, 95% CI 1.25–2.96), intracranial hemorrhage (ICH) (HR 3.51, 95% CI 1.40–8.76), and all-cause death (HR 1.60, 95% CI 1.13–2.25) compared with that in the lowest quartile, whereas they showed no significant risk of ischemic stroke or systemic embolism (SE) (HR 0.84, 95% CI 0.49–1.44) [14].

It is important to investigate the association between BP-VVV and clinical outcomes using BP data of patients with AF from two previous studies [8, 9] and the current study [14]. These results indicate that BP data in patients with AF could be useful for studies on BP-VVV, as well as those in

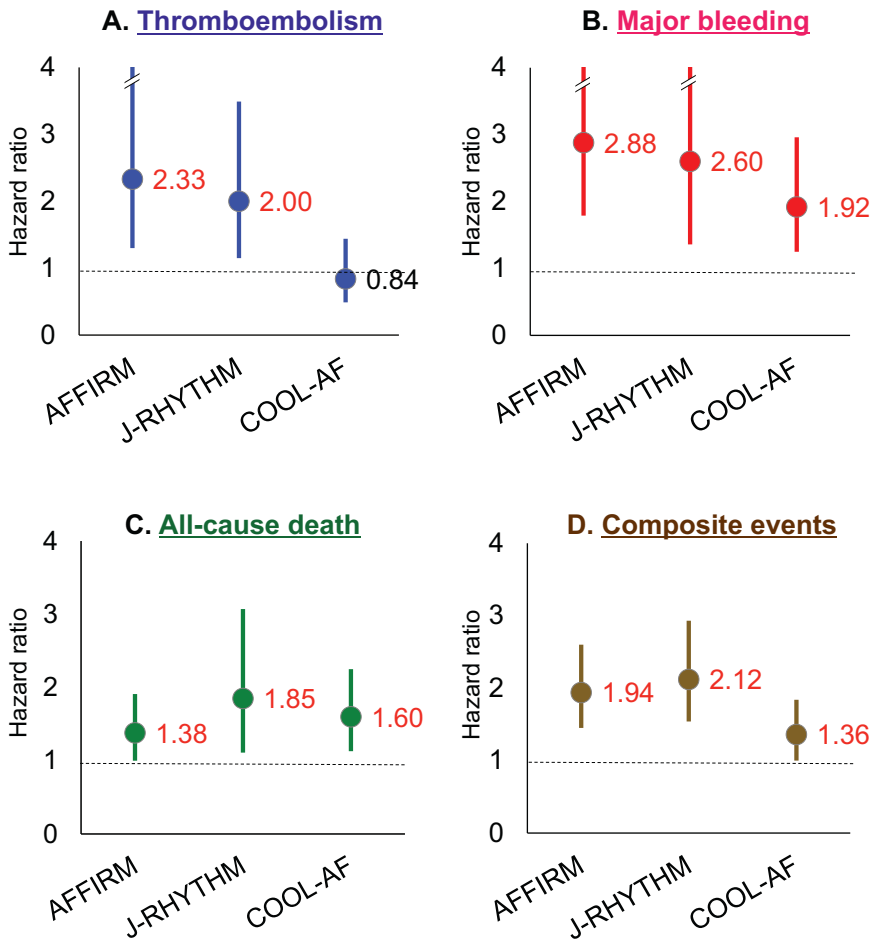

Fig. 1 Risk of the highest quartile (Q4) of systolic blood pressure (BP)-standard deviation (SD) on adverse events compared with the lowest quartile (Q1) in patients with atrial fibrillation (AF). **A**, Thromboembolism; **B**, Major bleeding; **C**, All-cause death; **D**, Composite events. AFFIRM Study [8]: Systolic BP-SD quartiles are Q1, <10.09; Q2, 10.09–13.85; Q3, 13.86–17.33; and Q4, ≥17.34 mmHg. Thromboembolism includes stroke while composite events include stroke, major bleeding, or cardiovascular death. Hazard ratios were adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack (TIA), myocardial infarction, peripheral arterial disease, sex, warfarin use, time in therapeutic range, hepatic/renal disease, pulmonary disease, and randomized treatment. J-RHYTHM Registry [9]: The systolic BP-SD quartiles are Q1, <8.20; Q2, 8.20–10.49; Q3, 10.50–13.19; and Q4, ≥13.20 mmHg. Thromboembolism includes ischemic stroke, TIA, or systemic embolism (SE), and composite events include ischemic stroke, TIA, or SE, major bleeding, or all-cause death. Hazard ratios were adjusted for congestive heart failure, hypertension, age, diabetes mellitus, stroke/TIA, coronary artery disease, sex, warfarin and antiplatelet use, AF type, BP measurement times, creatinine clearance, body mass index, and hemoglobin levels. COOL-AF Registry [14]: The systolic BP-SD quartiles are Q1, 0.58–9.09; Q2, 9.11–12.15; Q3, 12.17–16.21; and Q4, 12.17–16.21 mmHg. Thromboembolism includes ischemic stroke or SE, and composite events include ischemic stroke, SE, or all-cause death. Hazard ratios were adjusted for age, sex, AF type, symptomatic AF, baseline systolic BP, history of heart failure, coronary artery disease, cardiac implantable electronic device, history of stroke/TIA, hypertension, diabetes, smoking, dyslipidemia, renal replacement therapy, dementia, chronic kidney disease, history of bleeding, antiplatelet use, anticoagulant type and CHA_2DS_2-VASc score. For the analysis of major bleeding, the HAS-BLED score was included. Generated from [8, 9], and [14]

patients with sinus rhythm. The representative adjusted HRs in the highest quartiles compared to those in the lowest quartiles in these three studies, including the current study [14], are shown in Fig. 1. Recently, the impact of home BP on the risk of adverse events was reported in a subcohort study of the All Nippon AF in the Elderly (ANAFIE) Registry [15], in which home BP was measured twice, once in the morning and once in the evening, for 7 days using an oscillometric device with an arm cuff. In this study, a home systolic BP ≥ 145 mmHg was associated with an increased risk of stroke/SE, major bleeding, ICH, and net cardiovascular outcome compared to a home systolic BP < 125 mmHg. These results indicate that home BP data are also feasible for risk stratification, even in patients with AF.

Accordingly, AF would not become a reason to exclude patients from studies using BP data. In addition to patients with sinus rhythm, those with AF may be suitable target for studies on BP variability.

Compliance with ethical standards

Conflict of interest EK received remuneration from Daiichi-Sankyo. However, there are no conflicts of interest to declare.

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