Received: 31 May 2020 | Revised: 15 September 2020 | Accepted: 2 October 2020

DOI: 10.1111/jch.14095

ORIGINAL PAPER

WILEY

High prevalence of masked uncontrolled morning hypertension in elderly non-valvular atrial fibrillation patients: Home blood pressure substudy of the ANAFIE Registry

Kazuomi Kario MD, PhD[1] | Naoyuki Hasebe MD, PhD[2] | Ken Okumura MD, PhD[3] | Takeshi Yamashita MD, PhD[4] | Masaharu Akao MD, PhD[5] | Hirotsugu Atarashi MD, PhD[6] | Takanori Ikeda MD, PhD[7] | Yukihiro Koretsune MD, PhD[8] | Wataru Shimizu MD, PhD[9] | Hiroyuki Tsutsui MD, PhD[10] | Kazunori Toyoda MD, PhD[11] | Atsushi Hirayama MD, PhD[12] | Masahiro Yasaka MD, PhD[13] | Takenori Yamaguchi MD, PhD[11] | Satoshi Teramukai PhD[14] | Tetsuya Kimura MS[15] | Jumpei Kaburagi MS[15] | Atsushi Takita MS[16] | Hiroshi Inoue MD, PhD[17]

[1]Division of Cardiovascular Medicine, Jichi Medical University, Tochigi, Japan

[2]Department of Cardiology, Nephrology, Pulmonology and Neurology, Asahikawa Medical University, Hokkaido, Japan

[3]Division of Cardiology, Saiseikai Kumamoto Hospital, Kumamoto, Japan

[4]The Cardiovascular Research Institute, Tokyo, Japan

[5]Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan

[6]Minami Hachioji Hospital, Tokyo, Japan

[7]Department of Cardiovascular Medicine, Toho University Omori Medical Center, Tokyo, Japan

[8]National Hospital Organization Osaka National Hospital, Osaka, Japan

[9]Division of Cardiology, Nippon Medical School, Tokyo, Japan

[10]Department of Cardiovascular Medicine, Kyushu University, Fukuoka, Japan

[11]National Cerebral and Cardiovascular Center, Suita, Japan

[12]Osaka Police Hospital, Osaka, Japan

[13]Department of Cerebrovascular and Neurology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

[14]Department of Biostatistics, Kyoto Prefectural University of Medicine, Kyoto, Japan

[15]Medical Science Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

[16]Biostatistics and Data Management Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan

[17]Saiseikai Toyama Hospital, Toyama, Japan

Correspondence
Kazuomi Kario, MD, PhD, FACP, FACC, FAHA, FESC, Division of Cardiovascular Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan.
Email: kkario@jichi.ac.jp

Funding information
Daiichi Sankyo Co.

Abstract

In the ANAFIE Registry home blood pressure subcohort, we evaluated 5204 patients aged ≥75 years with non-valvular atrial fibrillation (NVAF) to assess blood pressure (BP) control, prevalence of masked hypertension, and anticoagulant use. Mean clinic (C) and home (H) systolic/diastolic BP(SBP/DBP) was 128.5/71.3 and 127.7/72.6 mm Hg, respectively. Overall, 77.5% of patients had hypertension; of these, 27.7%, 13.4%, 23.4%, and 35.6% had well-controlled, white coat, masked, and

sustained hypertension, respectively. Masked hypertension prevalence increased with diabetes, decreased renal function, age ≥80 years, current smoker status, and chronic obstructive pulmonary disease. By morning/evening average, 59.0% of patients had mean H-SBP ≥ 125 mm Hg; 48.9% had mean C-SBP ≥ 130 mm Hg. Early morning hypertension (morning H-SBP ≥ 125 mm Hg) was found in 65.9% of patients. Although 51.1% of patients had well-controlled C-SBP, 52.5% of these had uncontrolled morning H-SBP. In elderly NVAF patients, morning H-BP was poorly controlled, and masked uncontrolled morning hypertension remains significant.

1 | INTRODUCTION

While aging increases the incidence of AF dramatically, the greatest risk factor of AF is hypertension.[1,2] AF is not only the most common arrhythmia in the elderly,[3] but it predisposes individuals to an increased risk of embolic stroke.[4] The rapid expansion of the elderly population in many developed countries worldwide,[5] particularly in Japan,[6] has highlighted the need for data to guide the optimal management of patients with age-related comorbidities such as hypertension and AF.

It is widely known that hypertension worsens the prognosis of AF patients.[7] Our recent study revealed that blood pressure control status before the onset of AF defines the prognosis after the onset of AF, and early detection of silent AF in hypertensive patients is very important.[8-12] Further, in AF patients undergoing anticoagulation therapy, concomitant hypertension and poor blood pressure control increase both embolism and bleeding complications.[13-15] Therefore, it is recommended to control the blood pressure level of hypertensive patients during anticoagulation therapy to less than 130/80 mm Hg, as stated in recent Japanese, European, and American guidelines.[16-19]

Both domestic and international hypertension guidelines recommend blood pressure management based on measurements obtained outside the clinical setting, such as home blood pressure measurement or ambulatory blood pressure monitoring, which seem to be more closely related to organ damage and risk of cardiovascular events than blood pressure measurements obtained in the clinical setting.[11,16-26] Moreover, patients with masked hypertension have been shown to have a greater risk of stroke compared with patients with controlled blood pressure, even when the blood pressure measured in the clinical setting appeared well controlled.[27-31]

The HONEST and JHOP registry studies showed that early morning hypertension measured at home was a strong risk factor for stroke.[27-32] However, it is difficult to control morning blood pressure because of the limited 24-hour blood pressure-lowering effect of standard antihypertensive medication. Thus, a morning home blood pressure-guided individual approach is recommended for the management of hypertension.[32-35]

Circadian fluctuations in blood pressure and heart rate have been observed in AF patients and the elderly.[36-38] Further, AF patients seem to be more prone to stroke early in the morning.[39-42] To date, no study has examined blood pressure control status (especially in the morning) measured in the clinical and home settings in elderly NVAF patients. This subcohort study of patients from the ANAFIE Registry[35] evaluated blood pressure control and the prevalence of masked hypertension in elderly NVAF patients.

2 | METHODS

2.1 | Study design

The ANAFIE Registry (the University hospital Medical Information Network with the identifier UMIN000024006) was a multicenter, observational, prospective, longitudinal cohort study with an enrollment period between October 2016 and January 2018. The Registry aimed to collect information regarding the actual clinical status of elderly patients with NVAF (aged ≥ 75 years) in order to elucidate the current status of anticoagulant therapy and its clinical outcomes, to identify risk factors for death, thromboembolism, and major bleeding, as well as their interrelationships, and to establish a database for this specific patient population to aid in the development of therapeutic strategies. Full details of the ANAFIE Registry study design have been published.[35]

2.2 | Patients

Enrolled patients were elderly outpatients (≥75 years) diagnosed with NVAF by electrocardiogram who were able to visit the study site for specified visits. A proportion of patients included in the main ANAFIE study who already had an electric, oscillometric blood pressure monitoring device with arm cuff at home[29] were enrolled in this subcohort and all patients provided written informed consent to participate. No other specific enrollment conditions applied for inclusion in this subcohort. This subcohort study aimed to investigate the distribution of clinical features, blood pressure control, prevalence of masked hypertension, and use of anticoagulants.

2.3 | Measurement of blood pressure

Patients were provided guidance on the conditions, timing, and frequency of home blood pressure measurements. Home blood pressure

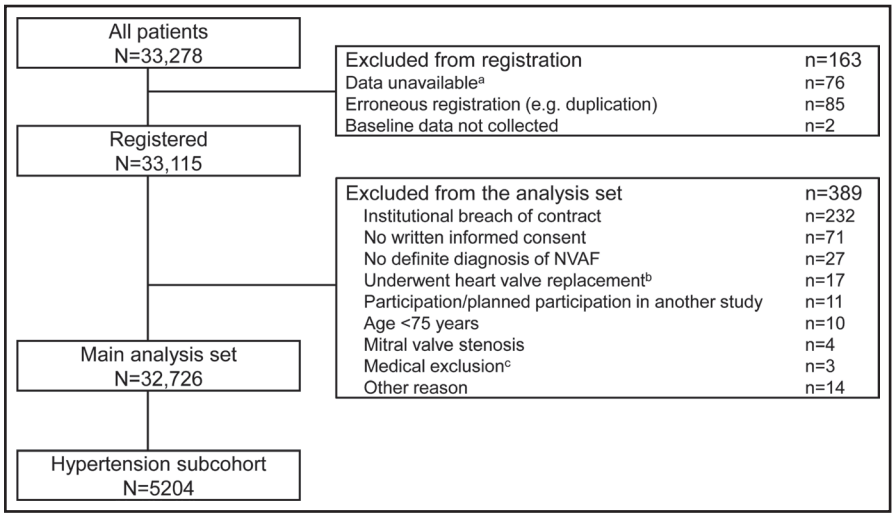


FIGURE 1 Patient disposition in the ANAFIE Registry home blood pressure subcohort. [a]Due to withdrawal of consent, discontinuation by physician/institution, or other reason. [b]Mechanical or bioprosthetic. [c]Development of cardiovascular or bleeding events requiring hospitalization within 1 month before enrollment. NVAF, non-valvular atrial fibrillation

was measured twice in the morning and twice in the evening for 7 days from the date of consent using an oscillometric blood pressure monitoring device with the cuff placed on the upper arm. Patients were required to record the home blood pressure readings in the home blood pressure recording sheet. However, if patients were unable to measure their blood pressure at home consecutively for 1 week, the measured value was recorded. Physicians then recorded the home systolic blood pressure (H-SBP) and home diastolic blood pressure (H-DBP) from the patients' home blood pressure recording sheet in the case report form as well as the clinic systolic blood pressure (C-SBP) and clinic diastolic blood pressure (C-DBP) (measured twice in one visit using a validated mercury, aneroid, or electronic sphygmomanometer as per the method routinely used at each institution). Distributions were calculated according to Japanese blood pressure guidelines[20] (H-SBP ≥ 125 or <125 mm Hg and C-SBP ≥ 130 or <130 mm Hg), estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2), smoking history, and chronic obstructive pulmonary disease (COPD). The proportion of patients with H-SBP ≥ 125 mm Hg by background characteristics (ie, age ≥ 80 years, diabetes, eGFR < 60 ml/min/1.73 m^2, smoking history, and COPD) was compared using morning measurements and the average of morning and evening measurements. These background characteristics were selected according to the risk factors for cerebrovascular and cardiovascular complications listed in the current Japanese Society of Hypertension Guidelines for the Management of Hypertension.[17]

2.4 | Statistical methods

Blood pressure was represented using the individual average levels of morning readings and the average of morning and evening readings. For this analysis, frequency tables were created for categorical variables, and summary statistics were calculated for continuous variables. More specifically, we averaged the two home blood pressure measurements that were reported by each patient at each designated time. We then averaged the home blood pressure results over 2 days. To calculate the average of morning and evening home blood pressure values, we used the morning and evening home blood pressure measured on the same day. The average of both clinic blood pressure measurements taken at each visit was also calculated. The home blood pressure and clinic blood pressure averages were then used to analyze relationships with clinical features, blood pressure control, prevalence of masked hypertension, and use of anticoagulants.

For categorical variables, *p*-values were calculated using the chi-squared test. For continuous variables, *p*-values were calculated using a two-sample *t* test or analysis of variance. A subgroup analysis was conducted based on home blood pressure status to determine the frequency of use of warfarin and each direct oral anticoagulant as well as to compare the proportions of patients with time in the therapeutic range (TTR) less than 40% by H-SBP < 125 mm Hg vs ≥ 125 mm Hg. In cases in which patients were unable to record their home blood pressure consecutively for 1 week, if a single measurement was taken during the week of evaluation, this single measured value was recorded and analyzed. Missing values were not replaced, and incomplete data (eg, outliers) were excluded from the analyses. A two-sided *p*-value <.05 was considered to indicate significance. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Tokyo, Japan).

3 | RESULTS

3.1 | Patient characteristics

Among the total analysis population of 32 726 elderly NVAF patients enrolled in the ANAFIE Registry, 5204 (15.9%) were included in the home blood pressure subcohort (Figure 1). In this subcohort

TABLE 1 Patient characteristics

	Home blood pressure subcohort *n* = 5204	Total ANAFIE population *N* = 32 726
Age, years	81.4 ± 4.8	81.5 ± 4.8
Male	2936 (56.4%)	18 733 (57.2%)
Height, cm	156.9 ± 9.5	157.2 ± 9.5
Weight, kg	57.7 ± 11.2	57.8 ± 11.2
Body mass index, kg/m^2	23.4 ± 3.6	23.3 ± 3.6
Ccr, ml/min	49.2 ± 18.1	48.4 ± 21.8
Clinic blood pressure, mm Hg		
Systolic	128.5 ± 17.2	127.4 ± 17.0
Diastolic	71.3 ± 11.5	70.6 ± 11.6
Home blood pressure, mm Hg[a]		
Systolic	127.7 ± 13.1	—
Diastolic	72.6 ± 9.1	—
Antihypertensive drug	3867 (74.3%)	23 180 (70.8%)
Comorbidities	5062 (97.3%)	31 826 (97.2%)
Hypertension	4035 (77.5%)	24 615 (75.2%)
Dyslipidemia	2244 (43.1%)	13 887 (42.4%)
Heart failure	1739 (33.4%)	12 262 (37.5%)
Gastrointestinal disorders	1609 (30.9%)	9584 (29.3%)
Diabetes mellitus	1342 (25.8%)	8833 (27.0%)
Cerebrovascular disorder	1172 (22.5%)	7410 (22.6%)
Hyperuricemia	1161 (22.3%)	7402 (22.6%)
Chronic kidney disease	965 (18.5%)	6787 (20.7%)
Angina	812 (15.6%)	5600 (17.1%)
Myocardial infarction	247 (4.7%)	1874 (5.7%)
Respiratory disease	591 (11.4%)	4194 (12.8%)
Malignant tumor	495 (9.5%)	3589 (10.9%)
Dementia	463 (8.9%)	2560 (7.8%)
Thromboembolic-related disease	414 (8.0%)	2809 (8.6%)
History of falls within one year	357 (6.9%)	2379 (7.3%)
Anticoagulant use	5204 (93.1%)	30 081 (91.9%)
Warfarin	1154 (22.2%)	8354 (25.5%)
Dabigatran	379 (7.3%)	2353 (7.2%)
Rivaroxaban	1234 (23.7%)	6463 (19.7%)
Apixaban	1265 (24.3%)	8085 (24.7%)
Edoxaban	811 (15.6%)	4813 (14.7%)
Non-oral anticoagulant	2 (0.0%)	40 (0.1%)
Other concomitant medication	5001 (96.1%)	31 045 (94.9%)
Antiarrhythmic drugs	2915 (58.3%)	18 374 (59.2%)
Antiplatelet drugs	872 (17.4%)	5793 (18.7%)
Hypolipidemic drugs	1976 (39.5%)	12 129 (39.1%)
Antidiabetic drugs	846 (16.9%)	5231 (16.8%)
Antidementia drugs	211 (4.2%)	1203 (3.9%)
Anticancer drugs	40 (0.8%)	289 (0.9%)
Anti-COPD drugs	126 (2.5%)	839 (2.7%)
Proton pump inhibitors	1901 (38.0%)	11 981 (38.6%)

Note: Data are shown as mean ± SD or *n* (%).

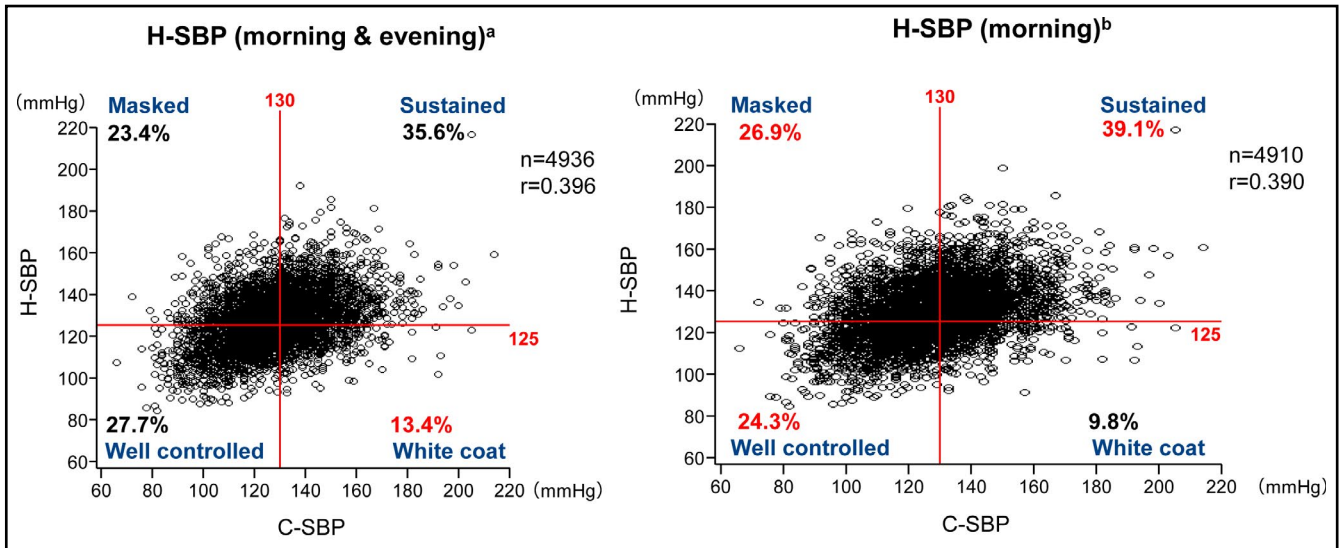
Abbreviations: Ccr, creatinine clearance; COPD, chronic obstructive pulmonary disease.

[a]Average of home blood pressure measured twice each morning and evening for 7 days from the date of consent.

population, the mean age was 81.4 years, the proportion of males was 56.4%, the body mass index (BMI) was 23.4 kg/m^2, and the eGFR was 54.9 ml/min/1.73 m^2 (Table 1). The mean ± SD blood pressure values in the subcohort were as follows: C-SBP, 128.5 ± 17.2 mm Hg; C-DBP, 71.3 ± 11.5 mm Hg; H-SBP, 127.7 ± 13.1 mm Hg; and H-DBP, 72.6 ± 9.1 mm Hg. The rate of hypertension in the subcohort was 77.5%, which was numerically higher than that in the overall population (75.2%), and 95.8% of patients with hypertension were receiving antihypertensive drugs (Table 1). In general, there were no notable differences between the subcohort and the total ANAFIE population (Table 1).

3.2 | Blood pressure control status

The H-SBP/H-DBP readings to calculate the average levels of morning blood pressure were performed 12.6 ± 2.8 times, and the morning and evening blood pressure readings were performed 24.7 ± 6.2 times. A total of 59.0% of patients had uncontrolled H-SBP ≥ 125 mm Hg according to the average of morning and evening blood pressure readings, while 48.9% had uncontrolled C-SBP ≥ 130 mm Hg (Figure 2, left; Table 2). Additionally, 65.9% of patients had uncontrolled H-SBP ≥ 125 mm Hg according to the average levels of morning blood pressure readings, while 48.9% had uncontrolled C-SBP ≥ 130 mm Hg (Figure 2, right; Table 2). Since this subcohort included 50 patients with four or fewer BP readings/week in the morning and evening and 68 patients with four or fewer BP readings/week in the morning, we removed them and outliers from this analysis.



	Type of hypertension			
H-SBP, n (%)	Well controlled	White coat	Masked	Sustained
Morning & evening[a]	1366 (27.7)	659 (13.4)	1154 (23.4)	1757 (35.6)
Morning[b]	1191 (24.3)	481 (9.8)	1319 (26.9)	1919 (39.1)

FIGURE 2 Prevalence of blood pressure control status according to type of hypertension and stratified by clinic and home blood pressure measurements. [a]Average home blood pressure measured twice each morning and evening for 7 days from the date of consent.Fifty patients with four or fewer home blood pressure readings/week in the morning and in the evening were excluded from this analysis. [b]Average home blood pressure measured twice in the morning for 7 days from the date of consent.Sixty-eight patients with four or fewer home blood pressure readings/week in the morning were excluded from this analysis. C-SBP, clinic systolic blood pressure; H-SBP, home systolic blood pressure

When blood pressure control was evaluated by type of hypertension (well controlled, masked, white coat, or sustained) according to C-SBP (< or ≥ 130 mm Hg) and H-SBP (< or ≥ 125 mm Hg), the population with masked hypertension was high, particularly in the morning (Figure 2; Table 3). In the analysis of H-SBP using the average of morning and evening blood pressure readings, 27.7% of patients had well-controlled, 13.4% had white coat, 23.4% had masked, and 35.6% had sustained hypertension. According to data on the average levels of morning blood pressure, the proportion of patients with masked hypertension was 26.9%, which was numerically higher than the proportion calculated using data on the average of morning and evening blood pressure readings. Even in those with well-controlled C-SBP (51.2% of total patients), 52.5% remained uncontrolled (>125 mm Hg) according to H-SBP based on average levels of morning blood pressure, that is, they had masked uncontrolled morning hypertension. When combined with patients with uncontrolled sustained hypertension, the overall rate of uncontrolled morning hypertension by H-SBP based on average levels of morning blood pressure was 65.9%.

The proportion of masked hypertension increased in patients with COPD (33.9%), diabetes (24.8%), and eGFR < 60 ml/min/1.73 m^2 (24.0%); in those aged ≥80 years (24.7%), and in current smokers (24.4%) (Table 3). The proportion of patients with morning H-SBP ≥ 125 mm Hg was numerically higher among patients aged ≥80 years than among those aged <80 years (67.1% vs 64.3%; Figure S1A); among those with diabetes than among those without diabetes (69.7% vs 64.6%; Figure S1B); among those with eGFR ≥60 ml/min/1.73 m^2 than among those with eGFR <60 mL/min/1.73 m^2 (69.2% vs 63.4%; Figure S1C). For all background characteristics, the rate of hypertension and the rate of home hypertension were higher with the average of morning blood pressure readings than with the average of morning and evening blood pressure readings. To determine whether the higher prevalence of morning hypertension among patients with diabetes and eGFR ≥ 60 ml/min/1.73 m^2 was influenced by age, we conducted further age-adjusted analysis. Among patients without diabetes, 53.9% (790/1467) of patients aged <80 years had H-SBP ≥ 125 mm Hg, while 59.7% (1330/2227) of those aged ≥80 years had H-SBP ≥ 125 mm Hg. Among patients with diabetes, 61.8% (355/574) of patients aged <80 years had H-SBP ≥ 125 mm Hg and 64.3% (461/717) of patients aged ≥80 years had H-SBP ≥ 125 mm Hg. Among patients with eGFR < 60 ml/min/1.73 m^2, 54.1% (538/995) of those aged <80 years had an H-SBP ≥ 125 mm Hg and 58.4% (1063/1819) of those aged ≥80 years had a H-SBP ≥ 125 mm Hg. Among patients

with eGFR ≥ 60 ml/min/1.73 m^2, 56.6% (419/740) of those aged <80 years had H-SBP ≥ 125 mm Hg while 63.8% (509/798) of those aged ≥80 years had H-SBP ≥ 125 mm Hg. From the above results, patients with eGFR <60 ml/min/1.73 m^2, as well as those with diabetes, tended to have higher H-SBP, regardless of age.

3.3 | Anticoagulation and blood pressure control

In this subcohort analysis, we conducted a subgroup analysis based on home blood pressure status to determine the frequency of use of warfarin and each direct oral anticoagulant as well as to compare the proportions of patients with TTR <40% by H-SBP < 125 mm Hg vs ≥ 125 mm Hg. We found that 93.1% of the patients were receiving anticoagulants (warfarin: 22.2%; direct oral anticoagulants: 70.9%); however, there was no significant difference between the H-SBP < 125 mm Hg and ≥ 125 mm Hg by type of anticoagulant therapy received (p > .05 [chi-squared test]) (Figure S2). In the warfarin group, the proportion of patients with TTR <40% was slightly higher in the H-SBP ≥ 125 mm Hg group than in the H-SBP < 125 mm Hg group (15.0% vs 10.9%, p = .0679 [chi-squared test]) (Figure S3).

4 | DISCUSSION

To the best of our knowledge, this is the first analysis of blood pressure control status measured in the clinical and home settings in elderly NVAF patients in Japan. Among 5204 elderly NVAF patients included in this home blood pressure subcohort of the ANAFIE study, most patients had hypertension (77.5%), and the use of antihypertensive drugs among these patients was high (95.8%).

In this home blood pressure subcohort, the average clinic and home blood pressure measurements were comparable. The mean C-SBP and C-DBP were 128.5 mm Hg and 71.3 mm Hg, while the mean H-SBP and H-DBP were 127.7 mm Hg and 72.6 mm Hg, respectively. Current Japanese guidelines emphasize the importance of achieving a strict blood pressure control for patients with AF, which is below 130/80 mm Hg in the clinical setting and below 125/75 mm Hg for home blood pressure.[17] AF and hypertension are both important risk factors for cardiovascular complications; however, these conditions are often found concomitantly. Particularly in patients with AF, the risk of complications such as stroke, arterial embolism, and all-cause death increases with increasing blood pressure.[20,43] Thus, it is necessary to maintain strict blood pressure control in patients with both AF and hypertension to prevent these complications. In the present home blood pressure subcohort, blood pressure control was generally in line with current guidelines,[17] as monitored in both the clinical setting and at home.

Two recent meta-analyses of blood pressure measurement in AF concluded that, despite the increased beat-to-beat blood pressure variability in AF patients, office blood pressure was clinically relevant[44] and, along with hypertension diagnosis, may be useful for predicting the risk of stroke or systemic embolism.[45] Interestingly, routine automated office, home, and ambulatory blood pressure measurements were all clinically relevant and resulted in a high diagnostic accuracy when used in conjunction with an AF-specific algorithm during screening.[44] It is also noteworthy that automated oscillometric blood pressure measurements appeared to be as

TABLE 2 Clinic and home blood pressure control status in the ANAFIE home blood pressure subcohort and in subgroups with different risk factors

		Risk factor				
	Subcohort total (n = 4985)	**Diabetes (n = 1291)**	**eGFR <60 ml/min/1.73 m^2 (n = 2904)**	**Age ≥ 80 years (n = 2944)**	**Current smoker[c] (n = 172)**	**COPD[c] (n = 124)**
C-BP, mm Hg			n = 2814			
Systolic ≥ 130	2438 (48.9%)	638 (49.4%)	1297 (46.1%)	1415 (48.1%)	89 (51.7%)	42 (33.9%)
Systolic < 130	2547 (51.1%)	653 (50.6%)	1517 (53.9%)	1529 (51.9%)	83 (48.3%)	82 (66.1%)
AV-ME H-BP, mm Hg[a]	n = 4936	n = 1287	n = 2788	n = 2913		
Systolic ≥ 125	2911 (59.0%)	814 (63.2%)	1590 (57.0%)	1777 (61.0%)	108 (62.8%)	75 (60.5%)
Systolic < 125	2025 (41.0%)	473 (36.8%)	1198 (43.0%)	1136 (39.0%)	64 (37.2%)	49 (39.5%)
AV-M H-BP, mHg[b]	n = 4910	n = 1282	n = 2775	n = 2900		
Systolic ≥ 125	3238 (65.9%)	894 (69.7%)	1759 (63.4%)	1946 (67.1%)	117 (68.0%)	85 (68.5%)
Systolic < 125	1672 (34.1%)	388 (30.3%)	1016 (36.6%)	954 (32.9%)	55 (32.0%)	39 (31.5%)

Note: Data are shown as n (%).

Abbreviations: C-BP, clinic blood pressure; COPD, chronic obstructive pulmonary disease; H-BP, home blood pressure.

[a]Average of home blood pressure measured twice each morning and evening for 7 days (AV-ME) and excluded 50 patients with four or fewer home blood pressure readings/week in the morning and evening.

[b]Average of home blood pressure measured twice in the morning for 7 days (AV-M) and excluded 68 patients with four or fewer home blood pressure readings/week in the morning.

[c]All subjects in this subcohort were analyzed.

TABLE 3 Blood pressure control status according to type of hypertension in the ANAFIE home blood pressure subcohort and in subgroups with different risk factors

		Risk factor				
	Subcohort total (*n* = 4985)	**Diabetes (*n* = 1291)**	**eGFR < 60 mL/min/1.73 m^2 (*n* = 2904)**	**Age ≥ 80 years (*n* = 2944)**	**Current smoker[c] (*n* = 172)**	**COPD[c] (*n* = 124)**
AV-ME control status[a]	*n* = 4936	*n* = 1287	*n* = 2788	*n* = 2913		
Well controlled	1366 (27.7%)	332 (25.8%)	830 (29.8%)	791 (27.2%)	41 (23.8%)	40 (32.3%)
White coat	659 (13.4%)	141 (11.0%)	368 (13.2%)	345 (11.8%)	23 (13.4%)	9 (7.3%)
Masked	1154 (23.4%)	319 (24.8%)	669 (24.0%)	719 (24.7%)	42 (24.4%)	42 (33.9%)
Sustained	1757 (35.6%)	495 (38.5%)	921 (33.0%)	1058 (36.3%)	66 (38.4%)	33 (26.6%)
AV-M control status[b]	*n* = 4910	*n* = 1282	*n* = 2775	*n* = 2900		
Well controlled	1191 (24.3%)	289 (22.5%)	750 (27.0%)	701 (24.2%)	35 (20.3%)	34 (27.4%)
White coat	481 (9.8%)	99 (7.7%)	266 (9.6%)	253 (8.7%)	20 (11.6%)	5 (4.0%)
Masked	1319 (26.9%)	362 (28.2%)	745 (26.8%)	805 (27.8%)	48 (27.9%)	48 (38.7%)
Sustained	1919 (39.1%)	532 (41.5%)	1014 (36.5%)	1141 (39.3%)	69 (40.1%)	37 (29.8%)

Note: Data are shown as *n* (%).

Abbreviations: COPD, chronic obstructive pulmonary disease; H-BP, home blood pressure; eGFR, estimated glomerular filtration rate.

[a]Average of home blood pressure measured twice each morning and evening for 7 days (AV-ME) and excluded 50 patients with four or fewer home blood pressure readings/week in the morning and evening.

[b]Average of home blood pressure measured twice in the morning for 7 days (AV-M) and excluded 68 patients with four or fewer home blood pressure readings/week in the morning.

[c]All subjects in this subcohort were analyzed.

clinically relevant as auscultatory blood pressure measurements in AF.[44] Further, both oscillometric and auscultatory blood pressure measurement methods were found to be similarly associated with indices of preclinical cardiac damage and predictive value for cardiovascular events and death.[44] These findings validate the use of the oscillometric blood pressure measurement method for measuring home blood pressure in this study.

In some patients with hypertension, a number of hemodynamic factors result in an early morning blood pressure surge and a prothrombotic state, characterized by atherothrombotic plaque vulnerability, endovascular shear stress, and increased coagulability; these factors have been associated with increased risk of cardiovascular events such as stroke and myocardial infarction, as well as bleeding events and vasculature damage.[46] In patients with AF, embolic and bleeding events occur commonly in the early morning, [39-41] so it is important to measure and control the blood pressure during this period of the day. In the present substudy, early morning home hypertension was present in over 60% of patients and the percentage of masked hypertension was more than 20% even when each was analyzed by background clinical characteristics. Further, for morning home blood pressure, the prevalence of masked hypertension was particularly high (up to 26.7%), and the proportion of patients with morning home blood pressure ≥125 mm Hg was 65.8%. In contrast, the JSH 2019 guidelines report that between 10% and 15% of non-hypertensive individuals in the general population have masked hypertension, while 9% to 23% of hypertensive patients whose clinic blood pressure is controlled to less than 140/90 mm Hg have masked hypertension.[17] Thus, the data resulting from home blood pressure measurements in our study suggest that masked hypertension may have been severely underestimated by prior reports that depended on clinic blood pressure measurements alone.

Systemic hemodynamic atherothrombotic syndrome (SHATS) is the result of the aging process and blood pressure fluctuations. SHATS leads to increased hemodynamic stress and causes vascular disease affecting small and large vessels.[46] In particular, continuous blood pressure fluctuation increases the risk of SHATS. AF is a typical model of blood pressure fluctuation, and elderly AF patients with advanced vascular stiffness are more susceptible to SHATS.[47,48] In order to reduce the risk of SHATS,[47] new NVAF events, and hemorrhagic and ischemic cardiovascular events[16] in these patients, it is paramount to aim for the best blood pressure control possible, particularly by reducing the morning blood pressure surges, as this parameter is closely related to cardiovascular disease.[28,47]

When comparing the present results with the primary results of the HONEST study,[29] patients in the ANAFIE home blood pressure subcohort had lower mean C-SBP (132.6 vs 128.5 mm Hg) and H-SBP (131.5 vs 127.7 mm Hg). Nevertheless, the prevalence of masked hypertension was high in this substudy, particularly in the morning; this finding is similar to that reported in the HONEST study. Another similarity with the HONEST study is that most patients with masked hypertension were receiving antihypertensive drugs. As in the present substudy, based on the average of morning and evening home blood pressure, HONEST study patients had insufficient control of morning H-SBP. Patients with severe

masked hypertension in the HONEST study were older, had cardiovascular comorbidities, and lower BMI.[8] A Finnish study evaluating similar associations also found that older age and current smoking were independent predictors of masked hypertension.[49] Our findings are consistent with that report, as the prevalence of masked hypertension was higher in patients with COPD, diabetes and eGFR <60 ml/min/1.73 m^2, those aged ≥80 years, and current smokers.

Notably, in this substudy of the ANAFIE population, ≥90% of patients received anticoagulation. In the group receiving warfarin, more patients with H-SBP ≥ 125 mm Hg than those with H-SBP < 125 mm Hg had a TTR < 40%, indicating that poor adherence to antihypertensive and anticoagulation treatment might have partly influenced home blood pressure control status. For patients with AF, Japanese guidelines (2019) recommend strict blood pressure control targeting a C-SBP < 130 mm Hg and H-SBP < 125 mm Hg in addition to anticoagulant therapy and heart rate control.[17] Thus, to reduce both embolic and hemorrhagic events, adequate anticoagulation with strict clinic and morning home blood pressure control is important, especially for elderly patients with stiffened arteries.

4.1 | Limitations

In common with all analyses from the ANAFIE Registry, the study limitations are mainly related to the observational, registry-based design.[50] As participation in the Registry was restricted to Japanese patients, it is also possible that the generalizability of the data to patient populations of other races may be limited. A limitation specific to this analysis was that clinic blood pressure was measured at only one visit. Although only SBP measurements were used to evaluate blood pressure control in this study, we do not perceive this to be a limitation, as SBP is more important than DBP in the elderly population. Additionally, as in AF, blood pressure fluctuates continuously, and this may affect the accuracy of the home blood pressure measurement. Further, home blood pressure monitoring might result in an overestimation of the blood pressure profile in selected elderly patients, such as those with orthostatic hypotension. More studies are needed to justify a strict home blood pressure target in very elderly patients. Finally, we did not study the relationship between home blood pressure and outcome; this relationship warrants further study in the future.

5 | CONCLUSIONS

Uncontrolled early morning hypertension (morning H-SBP ≥ 125 mm Hg) was found in 65.8% of patients aged ≥75 years with NVAF. Even in patients with C-SBP < 130 mm Hg, more than half had masked early morning hypertension according to H-SBP measurement. Among patients receiving warfarin, a higher proportion of patients with H-SBP ≥ 125 mm Hg had a TTR < 40 compared with those with H-SBP < 125 mm Hg. In high-risk elderly NVAF patients who receive anticoagulation, morning home blood pressure is still inadequately controlled, which is likely to result in an increased risk of both embolic and hemorrhagic stroke and cardiovascular events in the morning. However, the effects of increased morning home blood pressure will be further clarified in subsequent post-observation analyses.

ACKNOWLEDGEMENTS

This study was funded by Daiichi Sankyo Co., Ltd., Tokyo, Japan. The authors thank all individuals (physicians, nurses, institutional staff, and patients) involved in the ANAFIE Registry. They also thank IQVIA Services Japan KK and EP-CRSU for their partial support in the conduct of this Registry, and Sally-Anne Mitchell, PhD, and Keyra Martinez Dunn, MD, of Edanz Evidence Generation for providing medical writing support, which was funded by Daiichi Sankyo Co., Ltd., Tokyo, Japan.

CONFLICT OF INTEREST

Kazuomi Kario received research grants from Bristol-Myers Squibb, Bayer, Daiichi Sankyo, Omron Healthcare Inc, and A&D Inc, and remuneration from Daiichi Sankyo, Bayer, and Omron Healthcare Inc. Naoyuki Hasebe received research funding from Bristol-Myers Squibb and Daiichi Sankyo, and remuneration from Daiichi Sankyo and Bayer. Takeshi Yamashita received research funding from Bristol-Myers Squibb, Bayer, and Daiichi Sankyo, manuscript fees from Daiichi Sankyo and Bristol-Myers Squibb, and remuneration from Daiichi Sankyo, Bayer, Pfizer Japan, and Bristol-Myers Squibb. Masaharu Akao received research funding from Bayer and Daiichi Sankyo, and remuneration from Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Bayer, and Daiichi Sankyo. Hirotsugu Atarashi received remuneration from Daiichi Sankyo. Takanori Ikeda received research funding from Daiichi Sankyo and Bayer, and remuneration from Daiichi Sankyo, Bayer, Nippon Boehringer Ingelheim, and Bristol-Myers Squibb. Yukihiro Koretsune received remuneration from Daiichi Sankyo, Bayer, and Nippon Boehringer Ingelheim. Ken Okumura received remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and Medtronic. Wataru Shimizu received research funding from Bristol-Myers Squibb, Daiichi Sankyo, and Nippon Boehringer Ingelheim, and patent royalties/licensing fees from Daiichi Sankyo, Pfizer Japan, Bristol-Myers Squibb, Bayer, and Nippon Boehringer Ingelheim. Hiroyuki Tsutsui received research funding from Daiichi Sankyo, and Nippon Boehringer Ingelheim, remuneration from Daiichi Sankyo, Bayer, Nippon Boehringer Ingelheim, and Pfizer Japan, scholarship funding from Daiichi Sankyo, and consultancy fees from Pfizer Japan, Bayer, and Nippon Boehringer Ingelheim. Kazunori Toyoda and Hiroshi Inoue received remuneration from Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. Atsushi Hirayama participated in a course endowed by Boston Scientific Japan, and has received research funding from Daiichi Sankyo and Bayer, and remuneration from Bayer, Daiichi Sankyo, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. Masahiro Yasaka received research

funding from Nippon Boehringer Ingelheim, and remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Bayer, Bristol-Myers Squibb, and Pfizer Japan. Takenori Yamaguchi acted as an Advisory Board member of Daiichi Sankyo, and received remuneration from Daiichi Sankyo and Bristol-Myers Squibb. Satoshi Teramukai received research funding from Nippon Boehringer Ingelheim and remuneration from Daiichi Sankyo. Tetsuya Kimura, Jumpei Kaburagi, and Atsushi Takita are employees of Daiichi Sankyo.

AUTHOR CONTRIBUTIONS

KO, T Yamashita, MA, HA, TI, YK, WS, HT, KT, AH, MY, T Yamaguchi, and HI designed and conducted the study; KK and NH interpreted the data analysis; ST and AT carried out the statistical analyses; and KK, NH, KO, TK, and JK wrote and reviewed the manuscript. All authors revised and commented on the manuscript, and approved the final version.

ORCID

Kazuomi Kario https://orcid.org/0000-0002-8251-4480

REFERENCES

1. Aronow WS. Hypertension associated with atrial fibrillation. *Ann Transl Med*. 2017;5:457.
2. Verdecchia P, Angeli F, Reboldi G. Hypertension and atrial fibrillation: doubts and certainties from basic and clinical studies. *Circ Res*. 2018;122:352-368.
3. Curtis AB, Karki R, Hattoum A, Sharma UC. Arrhythmias in patients ≥80 years of age: pathophysiology, management, and outcomes. *J Am Coll Cardiol*. 2018;71:2041-2057.
4. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The epidemiology of atrial fibrillation and stroke. *Cardiol Clin*. 2016;34:255-268.
5. World Health Organization, National Institute on Aging, National Institutes of Health, U.S. Department of Health and Human Services. Global health and aging. NIH Publication no. 11–7737; October 2011. https://www.who.int/ageing/publications/global_health.pdf. Accessed December 17, 2019.
6. Japan Statistics Bureau, Ministry of Internal Affairs and Communications. Statistical Handbook of Japan 2018. http://www.stat.go.jp/english/data/handbook/pdf/2018all.pdf. Accessed December 17, 2019.
7. Panaich SS, Patel N, Agnihotri K, et al. A review of hypertension management in atrial fibrillation. *Curr Hypertens Rev*. 2016;12:196-202.
8. Kario K, Abe T, Kanegae H. Impact of pre-existing hypertension and control status before atrial fibrillation onset on cardiovascular prognosis in patients with non-valvular atrial fibrillation: a real-world database analysis in Japan. *J Clin Hypertens (Greenwich)*. 2020;2020(22):431-437.
9. Kabutoya T, Takahashi S, Watanabe T, et al. Diagnostic accuracy of an algorithm for detecting atrial fibrillation in a wrist-type pulse-wave monitor. *J Clin Hypertens*. 2019;21:1393-1398.
10. Kyriakoulis KG, Kollias A, Anagnostopoulos I, et al. Diagnostic accuracy of a novel cuffless self-blood pressure monitor for atrial fibrillation screening in the elderly. *J Clin Hypertens*. 2019;21:1797-1802.
11. Kario K, Shin J, Chen CH, et al. Expert panel consensus recommendations for ambulatory blood pressure monitoring in Asia: the HOPE Asia Network. *J Clinc Hypertens*. 2019;21:1250-1283.
12. Kario K, Tomitani N, Kanegae H, et al. The further development of out-of-office BP monitoring: Japan's ImPACT Program Project's achievements, impact, and direction. *J Clin Hypertens*. 2019;21:344-349.
13. Toyoda K, Yasaka M, Iwade K, et al. Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: a prospective, multicenter, observational study. *Stroke*. 2008;39:1740-1745.
14. Toyoda K, Yasaka M, Nagata K, et al. Bleeding with Antithrombotic Therapy Study Group: antithrombotic therapy influences location, enlargement, and mortality from intracerebral hemorrhage: the Bleeding with Antithrombotic Therapy (BAT) Retrospective Study. *Cerebrovasc Dis*. 2009;27:151-159.
15. Kodani E, Atarashi H, Inoue H, et al. Impact of blood pressure control on thromboembolism and major hemorrhage in patients with nonvalvular atrial fibrillation: a subanalysis of the J-RHYTHM Registry. *J Am Heart Assoc*. 2016;5:e004075.
16. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39:3021-3104.
17. Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension Guidelines for the management of hypertension (JSH 2019). *Hypertens Res*. 2019;42:1235-1481.
18. Kario K. Global Impact of 2017 American Heart Association/American College of Cardiology Hypertension Guidelines: a perspective from Japan. *Circulation*. 2018;137:543-545.
19. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:1269-1324.
20. Kario K, Wang JG. Could 130/80 mm Hg be adopted as the diagnostic threshold and management goal of hypertension in consideration of the characteristics of Asian populations? *Hypertension*. 2018;71:979-984.
21. Park S, Buranakitjaroen P, Chen CH, et al. Expert panel consensus recommendations for home blood pressure monitoring in Asia: the Hope Asia Network. *J Hum Hypertens*. 2018;32:249-258.
22. Kario K, Shimbo D, Hoshide S, et al. The emergence of home blood pressure-guided management of hypertension based on global evidence. *Hypertension*. 2019;74:229-236.
23. Kario K, Thijs L, Staessen JA. Blood pressure measurement and treatment decisions: masked and white coat hypertension. *Circ Res*. 2019;124:990-1008.
24. Kario K. *Essential manual on perfect 24-hour blood pressure management from morning to nocturnal hypertension: Up-to-date for anticipation medicine*. Tokyo, Japan: Wiley-Blackwell; 2018:1-309.
25. Joint Committee for Guideline Revision. 2018 Chinese Guidelines for Prevention and Treatment of Hypertension - a report of the Revision Committee of Chinese Guidelines for Prevention and Treatment of Hypertension. *J Geriatr Cardiol*. 2019;16:182-241.
26. Tong HY, Fan WG, Su H. The usefulness of 24-hour blood pressure monitoring for the patients with atrial fibrillation: based on the variability of blood pressure parameters. *Blood Press Monit*. 2020;25(22–25):27.
27. Hoshide S, Yano Y, Haimoto H, et al. Morning and evening home blood pressure and risks of incident stroke and coronary artery disease in the Japanese general practice population: The Japan Morning Surge-Home Blood Pressure Study. *Hypertension*. 2016;68:54-61.
28. Fujiwara T, Yano Y, Hoshide S, Kanegae H, Kario K. Association of cardiovascular outcomes with masked hypertension defined by home blood pressure monitoring in a Japanese general practice population. *JAMA Cardiol*. 2018;3:583-590.
29. Kario K, Saito I, Kushiro T, et al. Home blood pressure and cardiovascular outcomes in patients during antihypertensive therapy:

primary results of HONEST, a large-scale prospective, real-world observational study. *Hypertension*. 2014;64:989-996.
30. Kario K, Saito I, Kushiro T, et al. Morning home blood pressure is a strong predictor of coronary artery disease: the HONEST Study. *J Am Coll Cardiol*. 2016;67:1519-1527.
31. Kario K, Iwashita M, Okuda Y, et al. Morning home blood pressure and cardiovascular events in Japanese hypertensive patients. *Hypertension*. 2018;72:854-861.
32. Wang JG, Kario K, Chen CH, et al. Management of morning hypertension: a consensus statement of an Asian expert panel. *J Clin Hypertens (Greenwich)*. 2018;20:39-44.
33. Kario K, Park S, Buranakitjaroen P, et al. Guidance on home blood pressure monitoring: A statement of the HOPE Asia Network. *J Clin Hypertens (Greenwich)*. 2018;20:456-461.
34. Kario K, Park S, Chia YC, et al. 2020 Consensus summary on the management of hypertension in Asia from the HOPE Asia Network. *J Clin Hypertens (Greenwich)*. 2020;22(3):351-362. https://doi.org/10.1111/jch.13751
35. Inoue H, Yamashita T, Akao M, et al. Prospective observational study in elderly patients with non-valvular atrial fibrillation: rationale and design of the All Nippon AF In the Elderly (ANAFIE) Registry. *J Cardiol*. 2018;72:300-306.
36. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. *Sleep Med Rev*. 2012;16:151-166.
37. Yamashita T, Murakawa Y, Hayami N, et al. Relation between aging and circadian variation of paroxysmal atrial fibrillation. *Am J Cardiol*. 1998;82:1364-1367.
38. Deng M, Chen DW, Dong YF, et al. Independent association between age and circadian systolic blood pressure patterns in adults with hypertension. *J Clin Hypertens (Greenwich)*. 2017;19:948-955.
39. Lip GY, Tan EK, Lau CK, Kamath S. Diurnal variation in stroke onset in atrial fibrillation. *Stroke*. 2001;32:1443-1448.
40. Ripamonti L, Riva R, Maioli F, Zenesini C, Procaccianti G. Daily variation in the occurrence of different subtypes of stroke. *Stroke Res Treat*. 2017;2017:9091250.
41. Kawabori M, Niiya Y, Iwasaki M, et al. Characteristics of symptomatic intracerebral hemorrhage in patient receiving direct oral anticoagulants: comparison with warfarin. *J Stroke Cerebrovasc Dis*. 2018;27:1338-1342.
42. Peter-Derex L, Derex L. Wake-up stroke: from pathophysiology to management. *Sleep Med Rev*. 2019;48:101212.
43. Lip GY, Frison L, Grind M, et al. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J*. 2007;28:752-759.
44. Stergiou GS, Kyriakoulis KG, Stambolliu E, et al. Blood pressure measurement in atrial fibrillation: review and meta-analysis of evidence on accuracy and clinical relevance. *J Hypertens*. 2019;37:2430-2441.
45. Kollias A, Kyriakoulis KG, Stambolliu E, Stergiou GS. Prognostic value of office blood pressure measurement in patients with atrial fibrillation on anticoagulation therapy: systematic review and meta-analysis. *J Hypertens*. 2020;38:13-20.
46. Kario K, White WB. Early morning hypertension: what does it contribute to overall cardiovascular risk assessment? *J Am Soc Hypertens*. 2008;2:397-402.
47. Kario K, Chirinos JA, Townsend RR, et al. Systemic hemodynamic atherothrombotic syndrome (SHATS) – coupling vascular disease and blood pressure variability: proposed concept from Pulse of Asia. *Prog Cardiovasc Dis*. 2020;63:22-32.
48. Kario K. Systemic hemodynamic atherothrombotic syndrome (SHATS): diagnosis and severity assessment score. *J Clin Hypertens*. 2019;21:1011-1015.
49. Hänninen MR, Niiranen TJ, Puukka PJ, Mattila AK, Jula AM. Determinants of masked hypertension in the general population: the Finn-Home study. *J Hypertens*. 2011;29:1880-1888.
50. Koretsune Y, Yamashita T, Akao M, et al. Baseline demographics and clinical characteristics in the All Nippon AF in the Elderly (ANAFIE) Registry. *Circ J*. 2019;83:1538-1545.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kario K, Hasebe N, Okumura K, et al. High prevalence of masked uncontrolled morning hypertension in elderly non-valvular atrial fibrillation patients: Home blood pressure substudy of the ANAFIE Registry. *J Clin Hypertens*. 2021;23:73–82. https://doi.org/10.1111/jch.14095