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Pulse rate variability predicts atrial fibrillation and cerebrovascular events in a large, population-based cohort

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ABSTRACT

Background: Many patients with atrial fibrillation (AF) present with stroke as their first clinical manifestation and since improved AF screening methods are thus required, we investigated whether pulse rate variability parameters predict future AF and cerebrovascular events.

Methods: In an observational cohort study of 5000 community-resident adults (58% male; 50–84 years), the beat-to-beat variability of suprasystolic brachial blood pressure waveforms was measured with root mean square of successive differences (RMSSD) and irregularity index (IrrIx). Based on outcome-oriented and previously validated thresholds for detecting AF, RMSSD and IrrIx were dichotomised at 100 ms and 7.7%, respectively. Participants were followed up for 4.6 years (median), accruing 249 AF and 120 cerebrovascular events in the total sample (n = 5000), and 133 AF and 90 cerebrovascular events among those without prior AF diagnosis (n = 4296).

Results: In multivariable-adjusted analyses, an elevated RMSSD (>100 ms) or IrrIx (>7.7%) was strongly associated with a higher risk of AF (hazard ratios (HRs) = 2.00–2.95) and cerebrovascular events (HRs = 1.91–2.28), even among people without prior AF diagnosis: HRs for AF = 1.70–2.05 and cerebrovascular events = 2.00–2.28. These associations were strongest in the highest RMSSD tertile >100 ms or IrrIx tertile >7.7%: HRs for AF = 2.32–4.47 and cerebrovascular events = 2.43–3.69. Among those without prior AF diagnosis, the highest categorical net reclassification improvement for 5-year cerebrovascular risk was 14% (95% confidence interval: 7–21%).

Conclusions: Elevated RMSSD or IrrIx values indicative of the presence of AF predict future AF and cerebrovascular events; more so with increasing pulse irregularity and even among those without prior AF diagnosis.

1. Introduction

Atrial fibrillation (AF) is strongly associated with stroke incidence [1]. Many AF patients are asymptomatic and may present with stroke as their first clinical manifestation [2]. Thus, early AF detection is paramount. Opportunistic screening has been encouraged and has been shown to be more effective than routine practice and less costly than systematic screening with a 12-lead electrocardiogram (ECG) [3]. One opportunistic method is pulse palpation, but relies on subjective assessment in a busy clinical setting, it has limited diagnostic accuracy and is often not performed by doctors or nurses in clinical practice [4]. Therefore, improved opportunistic methods for early AF detection are warranted. For example, the 2016 European Society of Cardiology Guidelines recommends studies evaluating the diagnostic accuracy/yield of irregular pulse AF screening technologies [5]. This is becoming increasingly important due to the rising AF prevalence [5].

A potentially better approach to opportunistic screening is taking pulse rate variability (PRV) measurements with an electronic sphygmomanometer. Diagnostic studies show that these measurements accurately detect AF with high sensitivity and specificity [4,6]. A meta-analysis showed that, compared to other non-ECG AF screening devices, electronic blood pressure (BP) monitors have the highest diagnostic accuracy [7]. Thus, given that sphygmomanometer measurements are already routinely carried out in clinical practice, their additional use for AF screening could lead to earlier detection such that AF treatment may be administered sooner, with a likely improvement in patient outcomes (e.g., stroke prevention).

However, it is unknown how well PRV parameters measured using an electronic sphygmomanometer predict future AF and cerebrovascular events in the general population. Such information would yield new knowledge beyond ECG-based, cross-sectional, diagnostic studies [7]. First, if results of ECG studies based on non-general populations (e.g., outpatients) are applied to the general population, there may be

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some variation (and thus uncertainty) in screening performance due to the well-recognised spectrum effect [8]. Second, while all AF cases per se (ECG results in diagnostic studies [4,6]) are risk factors for prognostic outcomes [1], their ability to quantify the incidence/prevalence of AF-related hospitalizations is limited because: 1) not all result in hospital events [5] and, 2) hospitalizations occur at variable time-points. Thus, having AF and cerebrovascular events as endpoints would help to generate hypotheses about whether using BP monitors to earlier detect AF could reduce both hospitalizations for adverse health consequences of AF and the economic burden associated with treating AF in hospitals.

Therefore, we evaluated the relationships of PRV measurements (indicative of AF) with AF and cerebrovascular events. This included examining the associated improvement in cerebrovascular risk stratification to further assess the clinical usefulness of PRV. Given the expected increase in specificity for AF with increasing PRV and that many clinicians have postulated that rhythm control, while used exclusively to relieve symptoms (and increase quality of life), could potentially improve outcomes in AF [5,9,10], we also examined whether the level of PRV above thresholds deemed indicative of AF influenced these longitudinal associations.

2. Methods

2.1. Participants

The present study is an analysis of data collected in the ViDA study, a randomized controlled trial (RCT) of the health effects of vitamin D supplementation. Participants were recruited from family practices (predominantly) and community groups. Inclusion criteria were men and women aged 50–84 years and resident in Auckland at recruitment. Exclusion criteria included: 1) diagnosis of a terminal illness and/or in hospice care, 2) intending to leave New Zealand during the follow-up period, 3) taking vitamin D supplements (including cod liver oil) of >600 IU per day, 4) history of renal stones, hypercalcaemia, or medical conditions that can cause hypercalcaemia and/or 5) baseline serum calcium >2.50 mmol/L. Ethics approval was provided by the Ministry of Health Multi-region Ethics committee. Written, informed consent was obtained from each participant. Full details of the study design have been published elsewhere [11].

2.2. Non-BP measures

All measurements were performed by trained staff using a standardised protocol. Demographic, smoking and past medical history data were collected via questionnaires administered by interviewers. Past medical history was also captured from hospitalizations between August 2010 and the baseline evaluation (April 2011 to November 2012). Without shoes and in light clothing, height (±0.1 cm) was measured with a stadiometer weight (±0.1 kg) with digital scales. Body mass index (BMI) was calculated as body weight (kg)/height $(m)^2$. A blood sample was taken and centrifuged, and collected aliquots then stored at −80 °C (−112 °F) for later measurement of both serum total cholesterol and HDL (high-density lipoprotein) cholesterol on an Advia 2400 analyser (Siemens Healthcare Diagnostics, Germany).

Records of all hospitalizations (with ICD-10 coding) over the follow-up period (baseline to 30 September 2016) were collected from Ministry of Health databases and used to generate two endpoints: 1) AF events, which comprised hospitalizations for AF or atrial flutter (I48) and, 2) cerebrovascular events, which included hospitalizations for TIA (G459), ischemic stroke and other cerebrovascular events (including infarction, occlusion or stenosis) (I63–I68). All New Zealand residents are allocated a unique National Health Index number, which was used to track hospital admissions for these endpoints without our participants needing to attend post-baseline interviews.

2.3. BP measurements

After 15 minute rest while sitting, BP (±1 mm Hg) was measured three times with an Omron T9P oscillometric device (Omron Healthcare, Kyoto, Japan) placed above the cubital fossa of the left arm and the mean of the two closest measurements was used for analyses. Suprasystolic oscillometry was carried out using a BP+ device (Uscom, Sydney, Australia) (formerly known as a R6.5 cardiovascular monitor; Pulsecor, Auckland, New Zealand), with an appropriately-sized cuff positioned over the left upper arm. To improve the quality of the waveforms used in analyses, we decided a priori to exclude readings (n = 7; Supplemental Table 1) with a signal-to-noise ratio of <3 dB.

PRV was assessed from the variability of the beat duration of the suprasystolic pressure waveforms derived from the BP+ device using Custom-written Matlab software (Mathworks, Natick, MA). The waveforms spanned approximately 10 s; thus analysis was performed on approximately 10–12 pulse intervals. Two measures were used: root mean square of successive differences (RMSSD) and irregularity index (IrrIx). RMSSD (in ms) was calculated as the square root of the mean of the squared differences of the duration of successive pulse intervals [12]. IrrIx was calculated as standard deviation of pulse intervals as a percentage of the mean of these intervals [13,14]. In the calculations, we removed ectopic beats by excluding beats with duration below and above the 25th and 75th percentiles, respectively [13,14]. Representative pulse recordings from the BP+ device are illustrated in Supplemental Fig. 1.

2.4. Statistical analysis

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). As an RMSSD of >100 ms or IrrIx of >7.7% (measurements taken from a BP+ device; used in this study) have been found to identify patients with AF (determined via ECG tracings) with very high sensitivity and specificity [13], we hypothesized a priori that these PRV groups could be used to capture AF cases in our study. In support of this, prior AF diagnostic studies evaluating other BP monitors reported using a similar threshold for IrrIx (of 6%) [4,14]. To verify our hypothesis, we used a widely applied outcome-oriented approach, based on the log-rank test statistic, to determine PRV cut-points that most strongly correspond to AF events; the optimal threshold being where the absolute value of this test statistic is highest [15,16]. Supplemental Fig. 2 shows results of this analysis and, for RMSSD, the log-rank test statistic is almost maximal at RMSSD = 100 ms, and this threshold is close to and between the optimal cut-points in the total sample and among those without prior diagnosis of AF at baseline. For IrrIx, the optimal cut-point is ~8%, where the log-rank test statistic is highest. Therefore, to capture AF in subsequent analyses, we dichotomised RMSSD and IrrIx at 100 ms and 7.7%, respectively, since these values are appropriate thresholds.

Group differences in plots illustrating the cumulative proportion of people with events over time were examined using the log-rank test. Cox regression was used to evaluate associations of PRV measures with AF and cerebrovascular events. Multivariable AF models were adjusted for AF risk factors/scores, including CHARGE 5-year risk [17,18]. These scores included combinations of age, sex, ethnicity, antihypertensive use, heart failure, current smoking, diabetes, heart attack, weight, height, BMI, systolic BP (SBP), diastolic BP and pulse interval. Multivariable cerebrovascular models were adjusted for combinations of age, sex, ethnicity, smoking, diabetes, total:HDL cholesterol ratio, SBP and 5-year Framingham stroke risk [19]. In these cerebrovascular models for the total sample and in those without prior AF diagnosis, we also adjusted for prior cerebrovascular events. $CHADS_2$ and CHA_2DS_2-VASc scores are normally used to quantify or stratify stroke risk in AF patients [20], but as attempts have been made to extend these to the prediction of AF [21] and stroke/TIA in patients without AF too [22], we additionally included these in our AF and cerebrovascular prediction models. Monthly vitamin D supplementation had no apparent impact on cardiovascular events [23] and, thus, this factor was not included in multivariable models. In sensitivity analyses for these Cox models, we excluded people with low pulse rate (defined as <48 beats/min) as the associated relatively few number of beats (<8 over the ~10-second recording period) could potentially screen for AF less accurately.

To evaluate improvement in cerebrovascular risk stratification, we calculated net reclassification improvement (NRI). NRI represents the degree of correct reclassification of individuals into a lower or higher risk category when one prediction model is used instead of another [24]. It is the sum of the net percentage of individuals sustaining an event who are up-classified plus the net percentage of individuals not sustaining an event who are down-classified [24]. We calculated both categorical NRI, which is based on a finite number of risk groups, and continuous NRI, which uses an infinite number of risk categories. In the calculation of categorical NRI, as 5-year cerebrovascular risk for our participants was low (almost entirely <5% and a median of 2%), we chose four 5-year risk groups of <2.5%, 2.5–5%, 5–10% and >10%. These include categories that roughly correspond to low, moderate and high stroke risk groups used in decisions to initiate treatment to prevent stroke in AF patients [25]. A 2-tailed P-value of <0.05 was considered statistically significant.

3. Results

Supplemental Table 1 shows the characteristics of the participants at baseline in the total sample (n = 5000) and among those without prior diagnosis of AF at baseline (n = 4296). In both groups, age ranged from 50 to 84 years. Among people without prior AF diagnosis, 388 (9%) had an RMSSD > 100 ms *or* IrrIx > 7.7%.

The cohort was followed up for a median of 4.6 years (interquartile range: 0.7 years; range: 3.9–5.5 years). Over this period, 249 AF and 120 cerebrovascular events accrued in the total sample, while 133 AF and 90 cerebrovascular events occurred among those without prior AF diagnosis at baseline. AF was the primary or secondary reason for hospitalization in all AF events, with it being the main reason in 37% of cases, and other reasons being other cardiovascular (25%) and non-cardiovascular (38%) conditions (Supplemental Table 2).

3.1. Relationships with AF events

Supplemental Fig. 3 shows the cumulative proportion of individuals with an AF event over time according to high or low values of RMSSD (>100 ms or ≤100 ms) and IrrIx (>7.7% or ≤7.7%). In all participants

Table 1
Proportion of participants having an atrial fibrillation (AF) event during follow-up across pulse rate variability (PRV) groups and associated hazard ratios (95% CI).

Sample	PRV group	Number (%) of events	Model (covariates)					
			1: None	2: Age, sex, ethnicity	3: Ethnicity, $CHADS_2$ score	4: Ethnicity, CHA_2DS_2-VASc score	5: Ethnicity, CHARGE 5-year AF risk	6: Multiple AF risk factors[b]
Total (n = 5000)	RMSSD > 100 ms (n = 469)	64 (14)	3.60 (2.71, 4.78)	2.29 (1.70, 3.07)	2.74 (2.05, 3.67)	2.86 (2.14, 3.83)	2.66 (1.99, 3.56)	2.00 (1.47, 2.72)
	RMSSD ≤ 100 ms (n = 4531)[a]	185 (4)						
	IrrIx > 7.7% (n = 478)	65 (14)	3.62 (2.73, 4.80)	2.45 (1.83, 3.27)	2.86 (2.14, 3.81)	2.95 (2.21, 3.93)	2.65 (1.97, 3.57)	2.10 (1.54, 2.85)
	IrrIx ≤ 7.7% (n = 4522)[a]	184 (4)						
No prior AF (n = 4296)	RMSSD > 100 ms (n = 291)	19 (7)	2.38 (1.46, 3.86)	1.71 (1.04, 2.80)	2.03 (1.25, 3.31)	2.05 (1.26, 3.34)	1.87 (1.13, 3.08)	1.70 (1.01, 2.88)
	RMSSD ≤ 100 ms (n = 4005)[a]	114 (3)						
	IrrIx > 7.7% (n = 304)	19 (6)	2.27 (1.40, 3.69)	1.76 (1.07, 2.87)	2.00 (1.23, 3.25)	2.01 (1.23, 3.27)	1.95 (1.18, 3.21)	1.79 (1.07, 3.00)
	IrrIx ≤ 7.7% (n = 3992)[a]	114 (3)						

[a] Reference group.
[b] Age, sex, ethnicity, antihypertensive use, heart failure, current smoking, diabetes, heart attack, weight, height, systolic blood pressure, diastolic blood pressure, pulse interval.

and also in the large subset without prior AF diagnosis, having an AF event was significantly associated with these parameters, being higher in people with high RMSSD or IrrIx (all P < 0.001).

These differences also manifested in differences in event prevalence and hazard ratios (Table 1). Unadjusted analyses revealed that, among all participants, those with an RMSSD > 100 ms or IrrIx > 7.7% had over a 3.5-fold AF risk. After correction for combinations of demographics, stroke-risk scores ($CHADS_2$ or CHA_2DS_2-VASc), CHARGE 5-year risk and multiple AF risk factors, these associations attenuated but were still strong and positive (hazard ratios: 2.00–2.95). Among those without prior AF diagnosis, these relationships remained strong and positive (hazard ratios: 1.70–2.38).

In a sensitivity analysis, we excluded people (n = 237 or 5% of total sample) with a low pulse rate of <48 beats/min (Supplemental Table 3). This had variable impact on the HR points estimates, but mostly increased them, especially for RMSSD (by up to 0.25).

3.2. Relationships with cerebrovascular events

The cumulative proportion of people with a cerebrovascular event throughout the follow-up period by RMSSD and IrrIx index groups is illustrated in Supplemental Fig. 4. Both in all participants and those without prior AF diagnosis, having a cerebrovascular event was significantly related to these measures, with outcome being worst in those with RMSSD > 100 ms or IrrIx > 7.7% (all P ≤ 0.001).

Table 2 shows the proportion of participants having a cerebrovascular event during follow-up across PRV groups and the associated hazard ratios. Among all participants, unadjusted analyses showed that the risk of cerebrovascular events was >2.5-times higher in people with an RMSSD > 100 ms or IrrIx > 7.7%. These positive relationships were attenuated but remained significant after controlling for ethnicity and $CHADS_2$ or CHA_2DS_2-VASc score; and likewise after adjustment for age, sex, ethnicity, smoking, diabetes, total:HDL cholesterol ratio, SBP and prior cerebrovascular events. When the covariates were 5-year Framingham stroke risk, ethnicity and prior cerebrovascular events, cerebrovascular risk was >2-fold higher in those with high values of the PRV parameters. These associations were attenuated but still strongly positive when analyses were restricted to those without prior AF diagnosis (hazard ratios: 2.00–2.63) and among people without prior cerebrovascular events (hazard ratios: 2.33–3.17).

When we excluded those with a low pulse rate (<48 beats/min) in a sensitivity analysis, the HR points estimates noticeably increased for all associations, particularly for RMSSD and among those without prior cerebrovascular events (maximum HR increase of 0.61) or prior AF events (maximum HR increase of 0.72) (Supplemental Table 4).

3.3. Improvement in cerebrovascular risk prediction

We next examined whether the results for Table 2 translated into improvements in risk classification (Table 3). In those without prior

Table 2
Proportion of participants having a cerebrovascular event during follow-up across pulse rate variability (PRV) groups and associated hazard ratios (95% CI).

Sample	PRV measure	Number (%) of events	Model (covariates)				
			1: None	2: Ethnicity, $CHADS_2$ score	3: Ethnicity, CHA_2DS_2-VASc score	4: Age, sex, ethnicity, smoking, diabetes, TC/HDL-C, SBP[b]	5: 5-year Framingham stroke risk, ethnicity[b]
Total (n = 5000)	RMSSD > 100 ms (n = 469)	26 (6)	2.82 (1.82, 4.35)	2.07 (1.32, 3.23)	2.18 (1.40, 3.40)	1.91 (1.22, 2.98)	2.28 (1.46, 3.54)
	RMSSD ≤ 100 ms (n = 4531)[a]	94 (2)					
	IrrIx > 7.7%[b] (n = 478)	26 (5)	2.77 (1.79, 4.27)	2.12 (1.36, 3.30)	2.20 (1.41, 3.42)	2.00 (1.28, 3.12)	2.28 (1.47, 3.54)
	IrrIx ≤ 7.7% (n = 4522)[a]	94 (2)					
No prior AF (n = 4296)	RMSSD > 100 ms (n = 291)	14 (5)	2.63 (1.49, 4.65)	2.17 (1.22, 3.85)	2.23 (1.26, 3.96)	2.00 (1.12, 3.55)	2.28 (1.29, 4.04)
	RMSSD ≤ 100 ms (n = 4005)[a]	76 (2)					
	IrrIx > 7.7%[b] (n = 304)	14 (5)	2.51 (1.42, 4.44)	2.16 (1.22, 3.83)	2.18 (1.23, 3.87)	2.02 (1.14, 3.59)	2.17 (1.22, 3.85)
	IrrIx ≤ 7.7% (n = 3992)[a]	76 (2)					
No prior CBV events (n = 4762)	RMSSD > 100 ms (n = 419)	22 (5)	3.17 (1.97, 5.10)	2.74 (1.69, 4.43)	2.87 (1.78, 4.64)	2.33 (1.42, 3.80)	2.90 (1.80, 4.67)
	RMSSD ≤ 100 ms (n = 4343)[a]	76 (2)					
	IrrIx > 7.7%[b] (n = 432)	22 (5)	3.06 (1.90, 4.92)	2.67 (1.65, 4.32)	2.79 (1.73, 4.50)	2.33 (1.43, 3.79)	2.75 (1.70, 4.45)
	IrrIx ≤ 7.7% (n = 4330)[a]	76 (2)					

CBV = cerebrovascular; TC/HDL-C = total:HDL cholesterol ratio.
[a] Reference group.
[b] Prior CBV events were also adjusted for in total and "no prior AF" samples.

Table 3
Net reclassification improvement (NRI) values for cerebrovascular events (5-year risk) when pulse rate variability (PRV) measures are added to multivariable models.

Sample	Model	PRV measure added	Categorical NRI			Continuous NRI (95% CI)
			Net % with event up-classified	Net % without event down-classified	NRI (95% CI)	
Total (n = 5000)	1	RMSSD	14.2	−2.9	11.3 (3.5, 19.1)	26.7 (12.5, 40.9)
	1	IrrIx	14.5	−3.0	11.5 (3.7, 19.3)	26.3 (12.1, 40.6)
	2	RMSSD	13.3	−3.5	9.9 (2.2, 17.6)	26.7 (12.5, 40.9)
	2	IrrIx	14.5	−3.6	10.9 (3.0, 18.8)	26.3 (12.1, 40.6)
	3	RMSSD	10.3	−0.0	10.2 (1.9, 18.5)	22.9 (8.7, 37.2)
	3	IrrIx	7.0	0.5	7.5 (−1.4, 16.4)	22.1 (7.9, 36.4)
	4	RMSSD	16.5	−4.8	11.7 (3.3, 20.1)	26.6 (12.4, 40.9)
	4	IrrIx	15.6	−4.4	11.2 (2.5, 20.0)	26.3 (12.1, 40.6)
No prior AF (n = 4296)	1	RMSSD	11.4	−2.3	9.0 (1.8, 16.3)	19.0 (4.7, 33.4)
	1	IrrIx	11.6	−2.4	9.2 (1.9, 16.5)	18.4 (4.0, 32.8)
	2	RMSSD	15.2	−5.4	9.9 (2.4, 17.4)	19.0 (4.7, 33.4)
	2	IrrIx	15.4	−5.5	9.8 (2.3, 17.3)	18.4 (4.0, 32.8)
	3	RMSSD	12.5	−0.1	12.4 (4.8, 20.0)	18.5 (4.1, 32.8)
	3	IrrIx	13.8	0.3	14.1 (7.4, 20.8)	18.4 (4.0, 32.7)
	4	RMSSD	12.9	−3.3	9.6 (1.4, 17.8)	19.0 (4.6, 33.4)
	4	IrrIx	11.0	−3.1	7.8 (−0.9, 16.6)	18.4 (4.0, 32.7)
No prior CBV events (n = 4762)	1	RMSSD	22.5	−7.7	14.8 (6.6, 22.9)	29.4 (13.6, 45.2)
	1	IrrIx	22.5	−8.0	14.4 (6.3, 22.6)	28.8 (13.0, 44.6)
	2	RMSSD	3.3	6.3	9.6 (−2.5, 21.7)	29.4 (13.6, 45.2)
	2	IrrIx	4.0	4.4	8.4 (−3.6, 20.3)	28.8 (13.0, 44.6)
	3	RMSSD	10.8	0.7	11.6 (1.9, 21.3)	19.5 (3.5, 35.4)
	3	IrrIx	10.9	1.1	12.0 (2.3, 21.7)	25.2 (91.1, 41.3)
	4	RMSSD	15.7	−2.3	13.4 (3.5, 23.3)	29.4 (13.6, 45.2)
	4	IrrIx	12.4	−2.3	10.1 (−0.4, 20.6)	28.8 (13.0, 44.6)

IrrIx is dichotomised at 7.7%; RMSSD is dichotomised at 100 ms. Model 1 = Ethnicity, $CHADS_2$ score; model 2 = Ethnicity, CHA_2DS_2-VASc score; model 3 = Age, sex, ethnicity, smoking, diabetes, total:HDL cholesterol, SBP; model 4 = 5-year Framingham stroke risk, ethnicity. In models 3 and 4, prior CBV events were also adjusted for in total and "no prior AF" samples.

AF events, the addition of either PRV parameter to multivariable models improved predicted 5-year cerebrovascular risk classification, yielding categorical NRI values of 9–12% for RMSSD (dichotomised at 100 ms) and up to 14% for IrrIx (dichotomised at 7.7%). Similar improvements were observed in those without prior CBV events, with a highest categorical NRI of 15%. These improvements were predominantly due to the correct upward net reclassification of risk in individuals who had an event during follow-up. Larger improvements were observed with continuous NRI.

3.4. PRV stratification in AF

To examine the potential importance of the degree of PRV in AF, in the total sample, we stratified PRV parameters by approximate tertiles in the RMSSD > 100 ms and IrrIx > 7.7% groups (Fig. 1). Compared to participants with RMSSD ≤ 100 ms, those with progressively higher RMSSD above 100 ms (from 100–140 ms, 140–200 ms and then to >200 ms) had increasingly more AF (all $P < 0.001$ for trend) and cerebrovascular (all $P \leq 0.006$ for trend) risk. Similarly, with IrrIx ≤ 7.7% as the reference group, there was a stepwise increase in AF (all $P < 0.001$ for trend) and cerebrovascular (all $P \leq 0.02$ for trend) risk as IrrIx >7.7% increased from 7.7–9.5%, 9.5–12.5% and then to >12.5%. These associations were strongest in the highest RMSSD tertile (>200 ms) or IrrIx tertile (>12.5%), with hazard ratios ranging from 2.32 to 4.47 for AF events and 2.43 to 3.69 for cerebrovascular events.

4. Discussion

This longitudinal study of a population-based cohort (median follow-up of 4.6 years) showed that people with high values of RMSSD (>100 ms) or IrrIx (>7.7%) which have previously been shown to be indicative of AF presence [13], were more likely to have future AF and cerebrovascular events, even among people without prior diagnosis of AF. Second, these risk differences rose with increasing pulse irregularity above an RMSSD of >100 ms or above an IrrIx of >7.7. Finally, the addition of these PRV parameters to 5-year cerebrovascular risk prediction models improved risk classification in >10% of people.

To our knowledge, this is the first study to show that PRV parameters from a BP monitor predict future AF cases. Our findings are in agreement with diagnostic studies which demonstrated that high RMSSD and/or IrrIx values signify the presence of AF [4]. Some models have been developed to predict the risk of developing AF (new cases) [17]. However, we observed that, even after adjusting for these models in our analyses among those without prior AF diagnosis, RMSSD>100 ms and IrrIx > 7.7% were independently associated with an increased risk of AF events (Table 1). This indicates that these PRV parameters can predict future AF cases beyond existing risk models.

The positive relationships of high PRV measures with cerebrovascular events, even after controlling for established risk factors, also are original findings. The sizes of these hazard ratios varied from one model to another (Table 2) but were generally large. For example, independently of ethnicity, 5-year Framingham stroke risk and prior cerebrovascular events, in all participants with RMSSD > 100 ms, cerebrovascular risk was >2-times higher than among participants with RMSSD ≤100 ms (Table 2). Further, up to 15% of people with no prior cerebrovascular events were reclassified into more appropriate 5-year risk categories (<2.5%, 2.5–5%, 5–10% and >10%) when the binary RMSSD variable (dichotomised at 100 ms) was added to risk prediction models. Thus, the prognostic value of the PRV parameters appears likely to be clinically relevant. However, due to the wide NRI 95% confidence intervals (Table 3), we encourage similar reclassification analyses to be performed with more events in further studies to improve the precision of NRI estimates and thus verify clinical significance.

The finding that PRV measures predicted AF and cerebrovascular events in participants without prior diagnosis of AF is important. Such people represent those considered as being free of AF under current AF screening methods. As risk stratification was observed in these individuals (Tables 2 and 3), which translated into significant improvements in 5-year cerebrovascular risk classification (categorical NRI of up to 14%), these results collectively signify an improvement in the assessment of the prognosis of patients considered clinically to be free of AF.

Of our participants without prior AF diagnosis (n = 4296), 388 (9%) had an RMSSD > 100 ms *or* an IrrIx > 7.7%, indicating a potentially large

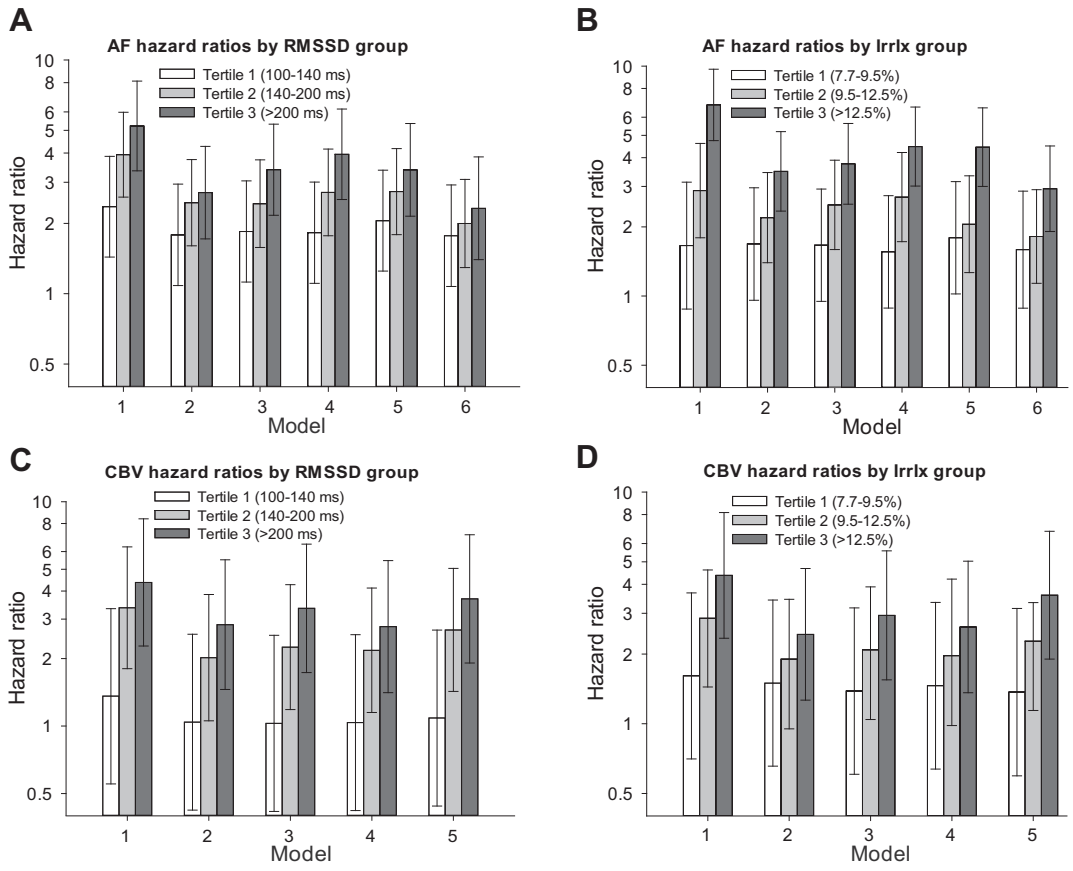

Fig. 1. Hazard ratios (95% CI), plotted on a log scale, for associations of RMSSD and IrrIx with AF and cerebrovascular (CBV) events. Tertiles of RMSSD > 100 ms are compared with RMSSD ≤ 100 ms (reference group). Tertiles of IrrIx > 7.7% are compared with IrrIx ≤ 100 ms (reference group). AF and CBV models are described in Tables 1 and 2, respectively.

number of undiagnosed AF cases. In support of this, population-based research has reported a sizeable prevalence of previously undiagnosed AF [26]. While our results mean that many individuals may benefit from earlier AF detection, this would be particularly so for those with a high stroke risk. Specifically, antithrombotic therapy (for stroke prevention) has been recommended for AF patients with a $CHADS_2$ score of ≥2 or with a CHA_2DS_2-VASc score of ≥1 (in males) or ≥2 (in females) [20]. Of the 388 potentially undiagnosed AF cases in our study, we estimate that 319 (82%) would meet the recommendations for consideration of antithrombotic therapy based on either of these scores. Together, these findings show that opportunistic screening for AF with PRV measurements could benefit numerous people by identifying a large number of undiagnosed cases, many of whom would especially benefit by receiving antithrombotic treatment.

The novel finding of stepwise increases in AF and cerebrovascular risk with increasing RMSSD >100 ms or IrrIx >7.7% (Fig. 1) may be due to various reasons. First, it could reflect an increase in the detection of *true* AF cases as higher PRV values are more likely to represent these. Second, higher PRV is easier to detect, which would lead to greater AF diagnosis and thus AF events. However, this would not account for the increase in cerebrovascular events. A third possible reason is that higher PRV in AF may be more symptomatic as rhythm-control drugs can help reduce AF-related symptoms associated with hospitalizations (e.g., for palpitations) [5]. Also, many have theorized that such drugs could potentially improve outcomes in AF [5,9,10] that might occur through preventing atrial remodelling [10], which is considered important in atrial thrombogenesis (and thus cerebrovascular risk) [27,28]. Although several trials do not support a beneficial effect on outcomes [10], better data are needed [29]. Of note, prior trials had a short follow-up period (0.5 to 3.5 years) and since AF is a progressive disease involving long-term remodelling, they may not have been long enough to demonstrate a beneficial effect of rhythm control [10]. Further, it has been hypothesized that, in AF, dysrhythmia causes atrial remodelling, thereby worsening atrial cardiopathy and increasing risk of thromboembolism [30]. Thus, whether our stepwise associations may potentially reflect these pathophysiological relationships is an idea that requires further investigation, which could involve determining whether the degree of PRV in AF screening and management should be monitored and is modifiable (e.g., via rhythm-control drugs).

5. Strengths and limitations

Strengths of the present study were that the sample was large and population-based, as most New Zealand residents (94%) are registered with a family practice [31]. Our ability to continuously track participants (using their unique National Health Index numbers) allowed us to comprehensively capture AF- and cerebrovascular-associated hospitalizations during follow-up. As for limitations, we did not distinguish between AF and atrial flutter, although we expect the former to dominate in our data as it is much more prevalent than atrial flutter [32]. Further, atrial flutter coexists with or precedes AF [33] and conveys thromboembolism, stroke and mortality risks [34], indicating the usefulness of identifying atrial flutter (in addition to AF). Another limitation is that our age range was limited to 50–84 years, but this would include ages that would more likely have AF.

6. Conclusions

In summary, elevated RMSSD and IrrIx values that are indicative of AF presence are associated with an increased number of AF and cerebrovascular events, even among people without prior AF diagnosis. This was more so with increasing PRV, implying prognostic importance of

the degree of pulse irregularity in AF which requires further research. The PRV parameters appear to be clinically useful as their addition to 5-year cerebrovascular risk prediction models improved risk classification of >10% of people. As these novel findings were present among people without prior AF diagnosis, they support performing these PRV measurements, which are easy and quick (~10 s) to perform, as this can earlier identify individuals who may have AF and/or are at risk of developing AF and cerebrovascular events so that therapeutic interventions (for stroke prevention) can be administered sooner. However, before widespread implementation, we encourage RCTs to clarify whether implementing these PRV measurements and consequent diagnostic and therapeutic interventions in clinical practice will truly lead to the expected improvements in AF-related health outcomes.

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Disclosure

Dr Lowe is a shareholder in and has consulted for Uscom Limited.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.026.

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