Risk Prediction of Atrial Fibrillation Based on Electrocardiographic Interatrial Block

Morten W. Skov, MD; Jonas Ghouse, MD; Jørgen T. Kühl, MD; Pyotr G. Platonov, MD, PhD; Claus Graff, MSc, PhD; Andreas Fuchs, MD, PhD; Peter V. Rasmussen, MD; Adrian Pietersen, MD; Børge G. Nordestgaard, MD, DMSci; Christian Torp-Pedersen, MD, DMSci; Steen M. Hansen, MD; Morten S. Olesen, MSc, PhD; Stig Haunsø, MD, DMSci; Lars Køber, MD, DMSci; Thomas A. Gerds, PhD; Klaus F. Kofoed, MD, DMSci; Jesper H. Svendsen, MD, DMSci; Anders G. Holst, MD, PhD; Jonas B. Nielsen, MD, PhD

Background—The electrocardiographic interatrial block (IAB) has been associated with atrial fibrillation (AF). We aimed to test whether IAB can improve risk prediction of AF for the individual person.

Methods and Results—Digital ECGs of 152 759 primary care patients aged 50 to 90 years were collected from 2001 to 2011. We identified individuals with P-wave ≥120 ms and the presence of none, 1, 2, or 3 biphasic P-waves in inferior leads. Data on comorbidity, medication, and outcomes were obtained from nationwide registries. We observed a dose-response relationship between the number of biphasic P-waves in inferior leads and the hazard of AF during follow-up. Discrimination of the 10-year outcome of AF, measured by time-dependent area under the curve, was increased by 1.09% (95% confidence interval 0.43−1.74%) for individuals with cardiovascular disease at baseline (CVD) and 1.01% (95% confidence interval 0.40−1.62%) for individuals without CVD, when IAB was added to a conventional risk model for AF. The highest effect of IAB on the absolute risk of AF was observed in individuals aged 60 to 70 years with CVD. In this subgroup, the 10-year risk of AF was 50% in those with advanced IAB compared with 10% in those with a normal P-wave. In general, individuals with advanced IAB and no CVD had a higher risk of AF than patients with CVD and no IAB.

Conclusions—IAB improves risk prediction of AF when added to a conventional risk model. Clinicians may consider monitoring patients with IAB more closely for the occurrence of AF, especially for high-risk subgroups. (***J Am Heart Assoc.*** 2018;7:e008247. DOI: 10.1161/JAHA.117.008247.)

Key Words: atrial fibrillation • ECG • epidemiology • interatrial • interatrial block • ischemic stroke • risk prediction

The electrocardiographic interatrial block (IAB) typically exists when a conduction delay over the Bachmann's bundle is present, however, it can also be caused by intra-atrial conduction delay and left atrial enlargement. By analogy to other types of block, there is a continuum of IAB severity; partial IAB is defined as a P-wave duration ≥120 ms and advanced IAB is defined as a P-wave duration ≥120 ms in conjunction with biphasic P-wave morphology in inferior leads II, III, and aVF.[1]

There has been an increasing interest in IAB in recent years, especially regarding its role in atrial fibrillation (AF) and ischemic stroke.[2] In previous prospective studies of the general population (N≈15 000), advanced IAB (yes/no) has been associated with an increased risk of AF and ischemic stroke.[3,4] The observed increased risk of ischemic stroke was reported to be independent of AF as an intermediate step.[4] For this reason, questions have been raised whether treatment with

<div style="border:2px solid red">

Clinical Perspective

What Is New?

- Electrocardiographic interatrial block (IAB) improves risk prediction of atrial fibrillation on an individual level; however, IAB does not seem to improve risk prediction of ischemic stroke.
- In general, individuals with advanced IAB and no cardiovascular disease had a higher risk of atrial fibrillation than patients with cardiovascular disease and no interatrial block.

What Are the Clinical Implications?

- Clinicians may consider intensified monitoring of patients with IAB for the occurrence of atrial fibrillation, especially if the block is advanced with biphasic P-waves in all inferior electrocardiographic leads.
- We would argue against initiating anticoagulation treatment merely on the presence of IAB, as suggested by others.

</div>

anticoagulation therapy in patients with IAB could be beneficial, regardless of AF status.[4,5] However, to properly assess the clinical utility of a parameter with regards to risk stratification, knowledge on the absolute risks of AF and ischemic stroke associated with IAB is needed. Moreover, whether IAB is of clinical value in long-term risks of AF and ischemic stroke on an individual level has not been investigated.

Using a large middle-aged and elderly population of primary care patients, we aimed to: (1) replicate earlier findings of an association between IAB and an increased risk of AF and ischemic stroke; (2) examine differences in hazards according to the number of biphasic P-waves in inferior leads; (3) investigate whether IAB is associated with conduction disorder and death from all causes; (4) evaluate whether IAB is of value in personalized long-term risk prediction of AF and ischemic stroke; (5) to estimate absolute risks of AF and ischemic stroke based on IAB across clinically relevant subgroups, and finally; (6) to describe the association between IAB and left atrial end-diastolic volume.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Population

This study is part of the Copenhagen ECG study encompassing all people who had an ECG recorded at the Copenhagen General Practitioners' Laboratory in the period 2001 to 2011,

as described in details previously.[6] For the present analyses, we excluded individuals with the following characteristics at baseline: <50 or ≥90 years of age, AF, ischemic stroke, treatment with class I or III anti-arrhythmic drugs, treatment with warfarin or non–vitamin K antagonist oral anticoagulants, and pacemaker or implantable cardioverter-defibrillator. Additionally, we excluded individuals with ECG findings inconsistent with interpretation of the IAB as noted in the Electrocardiography section.

According to Danish law, no approval from an ethics committee is needed in a registry-based study without any active participation from study subjects. The use of deidentified registry data was approved by the Danish Data Protection Agency.

Electrocardiography

All ECGs recorded at the Copenhagen General Practitioners' Laboratory were digitally stored in the MUSE® Cardiology Information System, and processed using version 21 of the Marquette 12SL algorithm (GE Healthcare, Wauwatosa, WI).[6] The Marquette 12SL algorithm is a ECG analysis program.[7] Using the 12SL algorithm, we excluded ECGs with rhythms different from sinus rhythm, multiple premature atrial or ventricular complexes, second- and third-degree atrioventricular blocks, heart rates <30 or >120 bpm, pace spikes, and ventricular preexcitation.[6] We divided the population into 5 categories based on IAB; normal P-wave duration (<120 ms), partial IAB (P-wave duration ≥120 ms and no biphasic [plus/minus] P waves in inferior leads) and 3 groups of IAB (P-wave duration ≥120 ms) associated with biphasic (plus/minus) P-waves in 1, 2, or 3 inferior leads (II, III, and aVF), the latter representing the strictly defined advanced IAB.[1,2] P-wave duration was obtained as previously described,[8] corresponding to the interval between the earliest detection of atrial depolarization in any lead and the latest detection of atrial depolarization in any lead. Amplitudes of significant waves within the P-wave are measured with respect to a baseline level that is interpolated from P onset to P offset. A wave crossing the baseline level which constitutes an area of ≥160 μV-ms is considered a separate and significant wave. The 12SL algorithm accommodates the phenomena of PR-interval depression. As such, IAB was defined by ourselves based on the 12SL algorithm's measurements of lead-specific amplitudes and global P-wave duration. Examples of IAB according to number of biphasic P-waves in inferior leads are illustrated in Figure 1. In a supplemental analysis, we also divided the population into eight categories based on which inferior leads, or combination of leads, were affected by a biphasic P-wave. We found excellent agreement between the 12SL algorithm and manual interpretation in the detection of IAB. We did an enriched random sampling of 25 normal ECGs, 25 with partial IAB, 25 with IAB
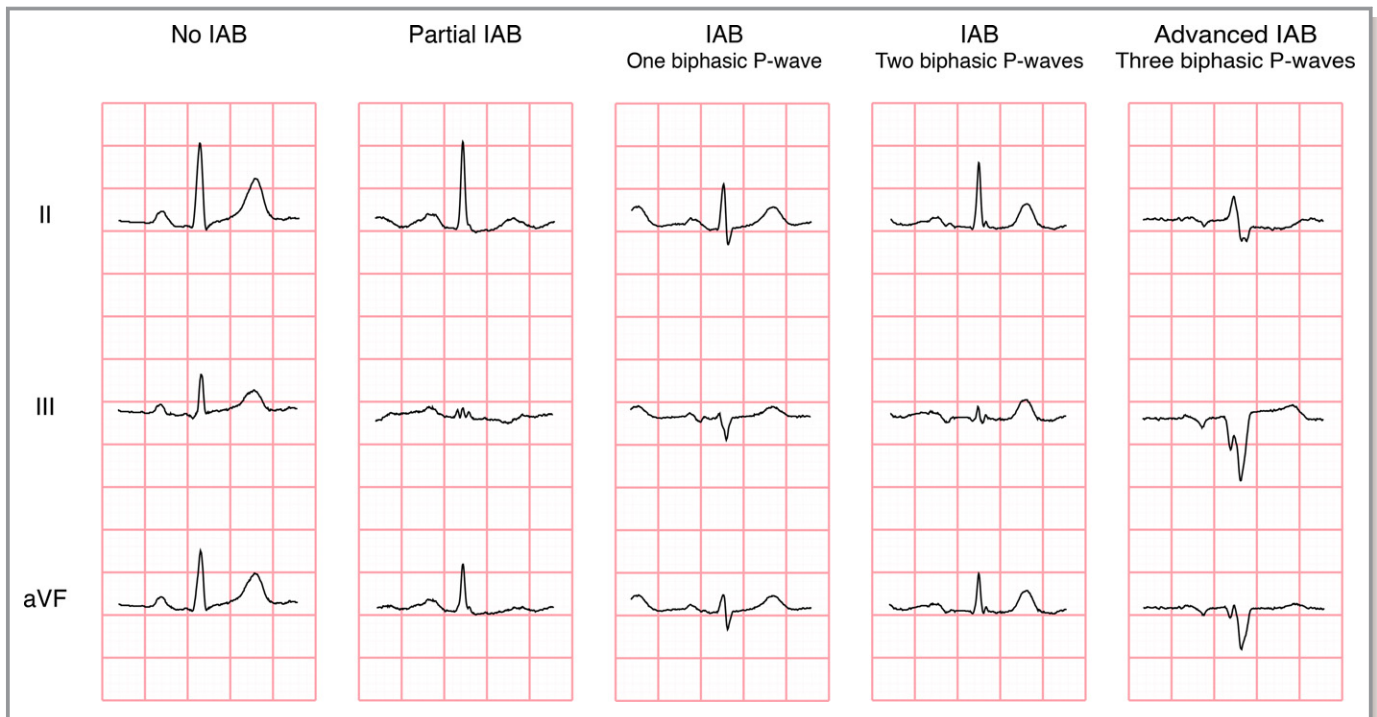
Figure 1. Examples of interatrial block as well as a normal ECG. IAB indicates interatrial block.

and 1 biphasic P-wave in inferior leads, 25 with IAB and 2 biphasic P-waves in inferior leads, and 25 with advanced IAB and 3 biphasic P-waves in inferior leads all detected by 12SL. Extraction of ECGs for the purpose of manual validation was done by C.G., manual interpretation of the ECGs blinded to the 12SL interpretation was done by M.W.S., and comparison between 12SL detected IAB and manual detected IAB was done by J.B.N. We observed an unweighted and weighted kappa of 0.98 (0.95–0.98) and 1.0 (0.99–1.0), respectively.

Baseline Variables and Follow-Up

All people with permanent residence in Denmark are allocated a unique and personal identification number which enables linkage of data across multiple nationwide healthcare registries. This makes it possible to gather information on death, emigration, the use of prescription medication and any hospital, outpatient clinic, or emergency room discharge diagnosis on an individual level.[9]

Individuals with the following characteristics at baseline were identified: hypertension, valvular heart disease, ischemic heart disease, heart failure (HF), diabetes mellitus, hyperthyroidism, obesity, sleep apnea, and anti-platelet use. Hypertension was defined from discharge diagnosis or if a subject before inclusion was treated simultaneously with at least 2 types of antihypertensive drugs.[10] Valvular heart disease was defined from discharge diagnosis, procedure, and operation codes.[10] Ischemic heart disease was defined

from discharge diagnoses of stabile angina pectoris or acute coronary syndrome. HF was defined as a discharge diagnosis of HF in combination with treatment with loop diuretics.[10] Diabetes mellitus and hyperthyroidism were defined from discharge diagnosis or in case of a purchase of prescription medication used for 1 of the 2 diseases. Obesity was defined from discharge diagnosis.[11] Anti-platelet use was defined from dispensed prescriptions. AF was the outcome of primary interest and was defined from hospital, outpatient clinic, or emergency room discharge diagnoses.[10] Secondary end points were ischemic stroke, death from all causes and a combined end point of sick sinus node syndrome and third degree atrioventricular block, named "conduction disorder" hereafter. Detailed information on the identification of covariates and clinical outcomes in the Danish registries is available in Tables S1 and S2. Follow-up began on the day of the first ECG recording (index ECG) and ended in case of the event of interest, death, emigration, or at December 31, 2013, whichever occurred first.

Cardiac Computed Tomography Scan Population

To determine the relationship between left atrial size and IAB, we included data from a population with available contrast enhanced low-dose cardiac computed tomography (CT) scans and digital ECGs. These individuals, randomly sampled from the general population in Copenhagen, were participants in the Copenhagen General Population Study.[12]

All cardiac CT scans were obtained in late diastole just before atrial contraction. Left atrial volume was manually assessed, as described in details previously.[13] A high degree of agreement with magnetic resonance imaging as well as a low interobserver variability has been observed.[13]

Written informed consent was obtained from all participants, and the study was approved by the local ethics committee (H-KF-01-144/01).

Statistical Analyses

Time-on-study was used as timescale in all survival analyses. The median follow-up time was estimated with the reverse Kaplan-Meier method.[14]

A 2-sided $P<0.05$ was considered statistically significant. All analyses were conducted with the use of Stata 14.0 software package (StataCorp LP, College Station, TX) and R (R Foundation for Statistical Computing, Vienna, Austria [URL http://www.R-project.org/]).

Association Analyses

Cause-specific Cox regression was used to assess the association of IAB on the index ECG with the hazard rate of AF, ischemic stroke, conduction disorder, and death, respectively, during follow-up. All Cox models were adjusted for age, sex, hypertension, valvular heart disease, ischemic heart disease, HF, diabetes mellitus, hyperthyroidism, obesity, sleep apnea, anti-platelet use, heart rate (categorized into tertiles), and Sokolow-Lyon ECG criteria of left ventricular hypertrophy. The category with a P-wave duration <120 ms (normal P-wave duration) was chosen as reference. In supplemental analyses individuals with 1 or 2 biphasic P-waves were further subdivided regarding which leads were affected. In this setting, the combination of 2 biphasic P-waves in leads II and III were excluded as only 6 individuals had this combination of 2 biphasic P-waves.

As a sensitivity analysis, the direct association between IAB and the risk of ischemic stroke, independent of AF as a possible intermediate step, was assessed by censoring individuals in case of incident AF.

Risk Prediction

Risk prediction analyses were conducted for 10-year outcome separately for individuals with and without cardiovascular disease (CVD) at baseline. CVD was defined as present if any of the following was present at baseline; valvular heart disease, HF, ischemic heart disease, or hypertension. The 10-year risks of AF and ischemic stroke were predicted in a competing risk setting by combining a Cox model for all-cause mortality and a Cox model for the outcome of interest.[15] The time-dependent

area under the receiving operating characteristics curve (AUC) was calculated to evaluate the added discriminative value of IAB for the purpose of AF- and ischemic stroke–specific risk prediction.[16] AUC corresponds to the probability that a person who experiences the event of interest (AF or ischemic stroke) within 10 years receives a higher predicted risk than that of a person who does not (dies or is alive 10 years after ECG). To estimate the 10-year AUC, we split the data into a training set (63%) and test set (37%). Since the results of this approach may depend on how the data are split, we split the data set 1001 times at random and then reported results for the split which corresponds to the median AUC in the 1001 models without IAB. Differences in AUC between models with and without IAB were calculated to assess the effect of adding IAB to conventional risk models for AF and ischemic stroke. Brier scores were calculated to evaluate model calibration.[17] To illustrate the time-trends of the predicted risks of AF and ischemic stroke, we calculated the average risks within 10-year age-groups for all combinations of CVD/no CVD and IAB pattern. Predictions for cumulative incidence curves were based on multivariable-adjusted Cox models fitted within the respective 10-year age-group and CVD subgroup (yes/no). Age within the various 10-year age-groups was included as a covariate.

Relationship Between IAB and Left Atrial Volume in the CT Study Population

Two approaches were used to describe the relationship between IAB and left atrial end-diastolic volume in the CT study population. First, the direct association between IAB and left atrial end-diastolic volume were descriptively assessed by means of a violin plot (comparing medians, interquartile range, range). Second, to adjust for age and sex differences across IAB subgroups, we constructed 2 logistic regression models with IAB as the outcome (yes/no): Model 1 included age and sex and model 2 included age, sex, and left atrial end-diastolic volume. AUC was calculated to compare the 2 models.

Results

A total of 343 607 individuals had an ECG recorded at the Copenhagen General Practitioners' Laboratory during the 11-year study period, and of these 152 759 (45%) individuals were eligible for inclusion. Baseline characteristics of the study population are presented in Table. In general, the more advanced IAB, the higher burden of comorbidity. The median follow-up time was 9.2 years (IQR 6.3–11.3). During follow-up, 12 657 people were diagnosed with incident AF, 13 497 were diagnosed with ischemic stroke, 2040 developed a conduction disorder, and 34 196 died.

Table. Baseline Characteristics

Characteristics	Interatrial Block				
	No IAB	Partial IAB	IAB, One Biphasic P-Wave	IAB, Two Biphasic P-Waves	Advanced IAB, Three Biphasic P-Waves
Total count—n (%)	113 204 (74)	24 403 (16)	11 888 (7.8)	2442 (1.6)	822 (0.5)
Age (y)—median (IQR)	63 (56–72)	65 (58–74)	66 (59–75)	72 (64–80)	78 (71–84)
Women—n (%)	69 199 (61)	12 045 (49)	4838 (41)	999 (41)	379 (46)
Medical history—n (%)					
Hypertension	25 995 (23)	7350 (30)	4386 (37)	1035 (42)	377 (46)
Valvular heart disease	359 (0.3)	111 (0.5)	62 (0.5)	23 (0.9)	9 (1.1)
Heart failure	952 (0.8)	302 (1.2)	178 (1.5)	53 (2.2)	38 (4.6)
Ischemic heart disease	7869 (7.0)	2051 (8.4)	1272 (10.7)	296 (12.1)	102 (12.4)
Diabetes mellitus	7306 (6.5)	1669 (6.8)	979 (8.2)	265 (10.9)	121 (14.7)
Hyperthyroidism	1770 (1.6)	420 (1.7)	179 (1.5)	40 (1.6)	14 (1.7)
Anti-platelets	17 655 (16)	4537 (19)	2679 (23)	664 (27)	270 (33)
Obesity	1713 (1.5)	447 (1.8)	296 (2.5)	57 (2.3)	31 (3.8)
Sleep apnea	500 (0.4)	132 (0.5)	103 (0.9)	17 (0.7)	4 (0.5)
CHA_2DS_2 VASc					
0 points	51 428 (45.4)	8846 (36.2)	3675 (30.9)	445 (18.2)	55 (6.7)
1 point	11 650 (10.3)	3528 (14.5)	2087 (17.6)	406 (16.6)	87 (10.6)
≥2 points	50 126 (44.3)	12 029 (49.3)	6126 (51.5)	1591 (65.2)	680 (82.7)
ECG variables					
Heart rate (bpm)—median (IQR)	71 (63–80)	71 (63–83)	68 (61–77)	68 (61–76)	70 (62–80)
Left ventricular hypertrophy—n (%)	3910 (3.4)	1415 (5.7)	606 (5.0)	178 (7.1)	59 (7.0)

For all baseline variables, except hyperthyroidism (P=0.56), we found that the observed differences in medians and proportions were statistically significantly ($P<0.001$) different across the 5 IAB-defined subgroups when calculating P for trend. Ischemic stroke is not included in CHA_2DS_2 VASc since individuals with ischemic stroke were excluded at baseline. ECG indicates electrocardiogram; IAB, interatrial block; IQR, interquartile range.

For lead specific distribution of 1 or 2 biphasic P-waves in inferior leads, please see Table S3. The most common inferior lead affected by a biphasic P-wave was lead III.

Association Analyses in the Whole Population

In general, we observed a dose–response association between the number of biphasic P-waves in inferior leads and the hazard of the various outcomes investigated (Figure 2). The associations were particularly strong with respect to development of AF and other conduction disorders. For advanced IAB, the hazard ratio was 3.38 (95% confidence interval [CI], 2.99–3.81) for developing AF, 1.45 (95% CI, 1.23–1.70) for developing ischemic stroke, 3.27 (95% CI, 2.52–4.23) for developing conduction disorder, and 1.35 (95% CI, 1.23–1.47) for all-cause mortality compared with the population without IAB. The association with the hazard rate of ischemic stroke was maintained when AF was considered a competing risk (Table S4). The association analyses considering which inferior leads were affected by a biphasic P-wave, or

combinations hereof, and the hazard rate of the various outcomes are presented in Figure S1. In general, the association with AF, ischemic stroke, and conduction disorder were particularly strong for combinations involving a biphasic P-wave in inferior lead II.

Risk Prediction of Atrial Fibrillation and Ischemic Stroke

Figure 3 displays the differences in AUC for the 10-year outcomes of AF and ischemic stroke obtained by adding IAB to conventional risk models for AF and ischemic stroke, respectively. Adding IAB to a conventional risk model for AF significantly increased AUC for the 10-year risk of AF in both groups of individuals: with CVD (difference in AUC, 1.09%: 95% CI, 0.43–1.74%) and without CVD at baseline (difference in AUC, 1.01%: 95% CI, 0.40–1.62%). For ischemic stroke as outcome, no significant changes in AUC for the 10-year prediction of ischemic stroke in both individuals with and without CVD at baseline were observed when adding IAB to a
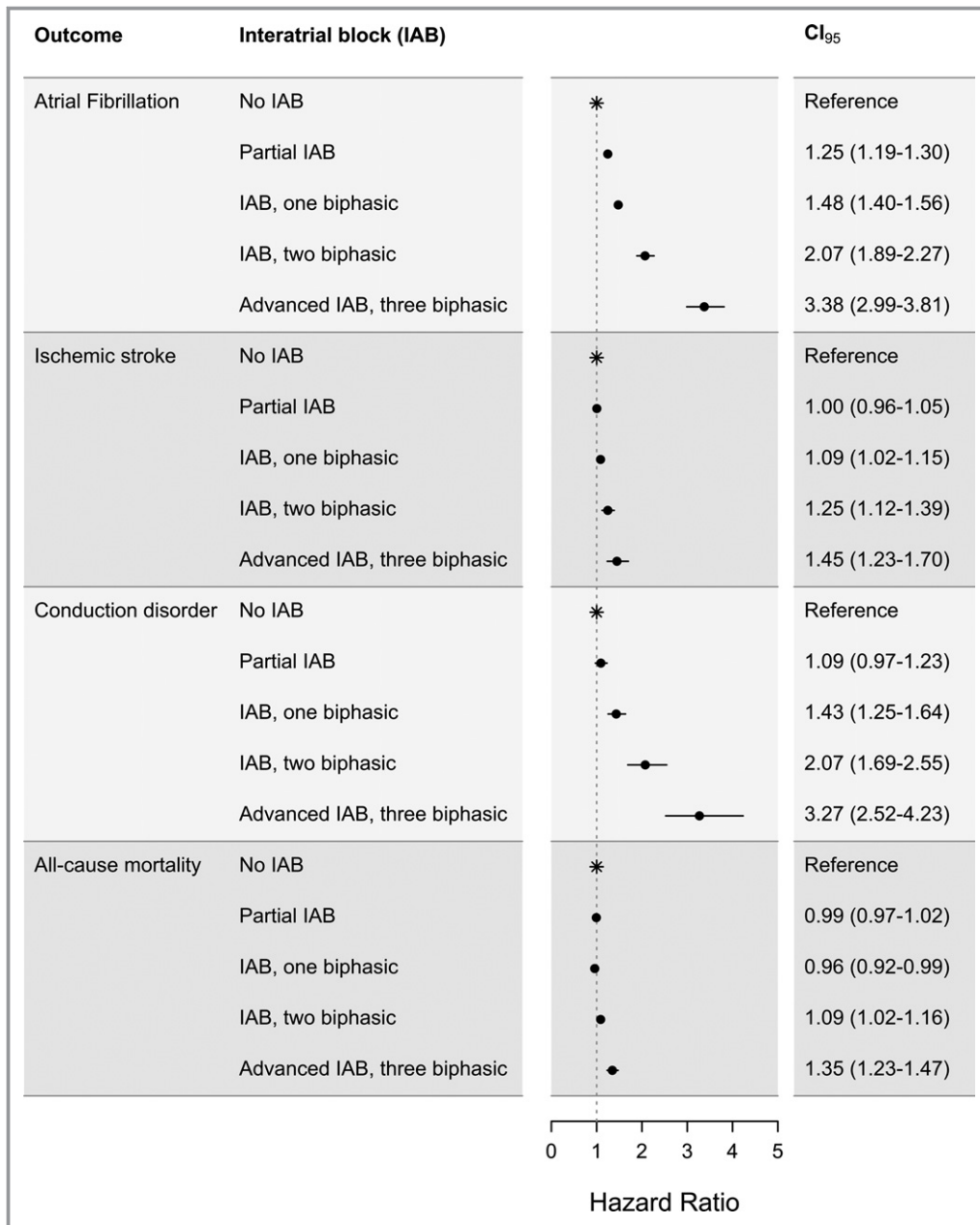
Outcome	Interatrial block (IAB)		CI95
Atrial Fibrillation	No IAB		Reference
	Partial IAB		1.25 (1.19-1.30)
	IAB, one biphasic		1.48 (1.40-1.56)
	IAB, two biphasic		2.07 (1.89-2.27)
	Advanced IAB, three biphasic		3.38 (2.99-3.81)
Ischemic stroke	No IAB		Reference
	Partial IAB		1.00 (0.96-1.05)
	IAB, one biphasic		1.09 (1.02-1.15)
	IAB, two biphasic		1.25 (1.12-1.39)
	Advanced IAB, three biphasic		1.45 (1.23-1.70)
Conduction disorder	No IAB		Reference
	Partial IAB		1.09 (0.97-1.23)
	IAB, one biphasic		1.43 (1.25-1.64)
	IAB, two biphasic		2.07 (1.69-2.55)
	Advanced IAB, three biphasic		3.27 (2.52-4.23)
All-cause mortality	No IAB		Reference
	Partial IAB		0.99 (0.97-1.02)
	IAB, one biphasic		0.96 (0.92-0.99)
	IAB, two biphasic		1.09 (1.02-1.16)
	Advanced IAB, three biphasic		1.35 (1.23-1.47)

Hazard Ratio (axis: 0 1 2 3 4 5)

Figure 2. Multivariable-adjusted hazard ratios for atrial fibrillation, ischemic stroke, conduction disorder, and all-cause mortality by interatrial block. CI95 indicates 95% confidence interval; IAB, interatrial block.

conventional risk model for ischemic stroke. Brier scores were significantly lower for models with IAB compared with conventional risk models for both AF and ischemic stroke as outcome.

Absolute Risk of Atrial Fibrillation and Ischemic Stroke

The median absolute risks of AF and ischemic stroke within the respective age- and CVD-groups are provided in Figures 4 and 5, respectively. The highest absolute risk of AF was observed for individuals with advanced IAB (3 biphasic P-waves) and CVD in the age-group 60 to 70 years. A total of 50% of the individuals in this subgroup developed AF within 10 years of follow-up compared with 10% in those with normal P-wave. The importance of IAB for individual risk predictions of AF within 1, 5, and 10 years from ECG according to different risk profiles is illustrated in Table S5.

With stroke as the outcome, the highest absolute risks were observed in those with advanced IAB (3 biphasic P-waves) and CVD aged 60 to 70 years and in those with no CVD aged 80 to 90 years, respectively. In these subgroups, the absolute risks of developing ischemic stroke during 10 years of follow-up were 20% and 25%, respectively,
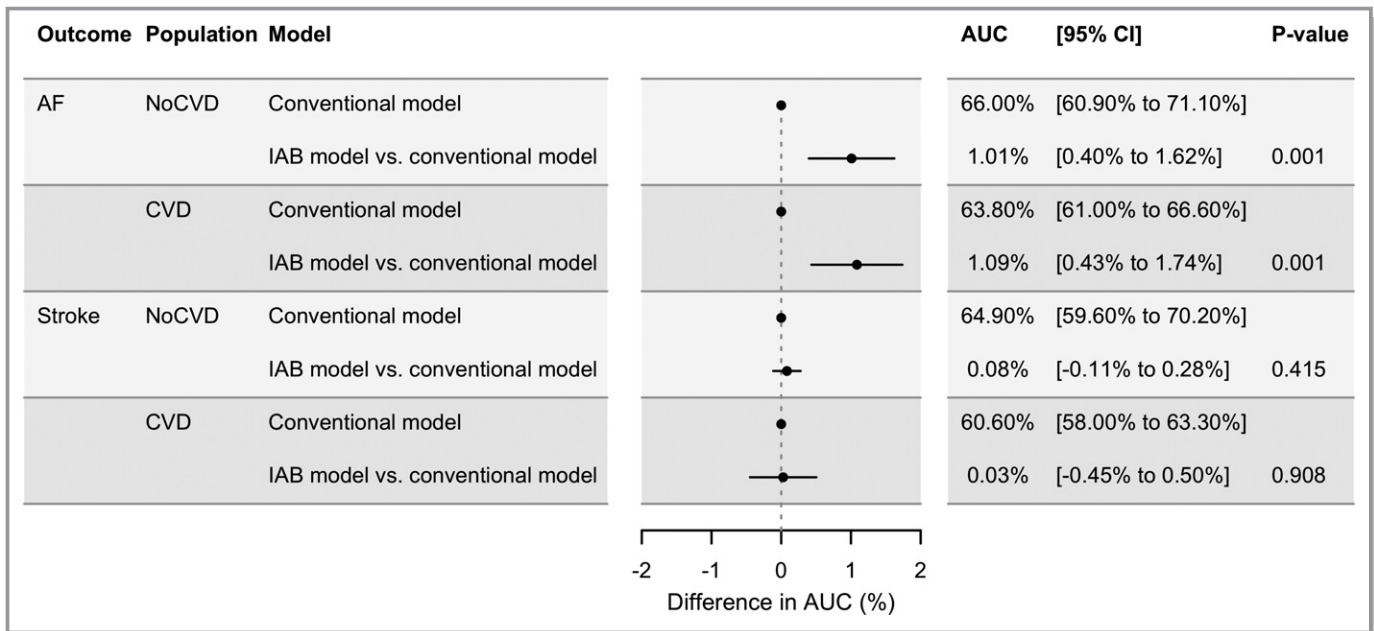
Outcome	Population	Model		AUC	[95% CI]	P-value
AF	NoCVD	Conventional model		66.00%	[60.90% to 71.10%]	
		IAB model vs. conventional model		1.01%	[0.40% to 1.62%]	0.001
	CVD	Conventional model		63.80%	[61.00% to 66.60%]	
		IAB model vs. conventional model		1.09%	[0.43% to 1.74%]	0.001
Stroke	NoCVD	Conventional model		64.90%	[59.60% to 70.20%]	
		IAB model vs. conventional model		0.08%	[-0.11% to 0.28%]	0.415
	CVD	Conventional model		60.60%	[58.00% to 63.30%]	
		IAB model vs. conventional model		0.03%	[-0.45% to 0.50%]	0.908

Difference in AUC (%): -2 -1 0 1 2

Figure 3. Differences in area under the curve for the 10-year outcomes of atrial fibrillation and ischemic stroke obtained by adding interatrial block to conventional risk models for atrial fibrillation and ischemic stroke, respectively, stratified by the presence or absence of cardiovascular disease at baseline. AF indicates atrial fibrillation; AUC, area under the curve; CI, confidence interval; CVD, cardiovascular disease at baseline; IAB, interatrial block; noCVD, no cardiovascular disease at baseline.

compared with 11% and 16% in those with normal P-wave, respectively.

For median absolute risk of conduction disorder within the respective age- and CVD-subgroups, see Figure S2.

Relationship Between IAB and Left Atrial Volume in the CT Study Population

A total of 5051 individuals had a cardiac CT and ECG obtained in sinus rhythm. The median age was 59 years (IQR 51–67 years), and 54% were women. Figure 6A displays the relationship between varying degrees of IAB and left atrial end-diastolic volume without taking age and sex into account. The more advanced IAB, the greater the left atrial end-diastolic volume. Figure 6B shows the receiving operator curve for 2 models predicting IAB (yes/no). The AUC was 65% for the model containing age and sex, whereas the AUC was 70% for the model containing age, sex, and left atrial end-diastolic volume.

Discussion

In this large ECG population, we: (1) confirmed previous findings of an association between IAB and AF and ischemic stroke; (2) presented novel findings of an association between IAB and conduction disorder; (3) found that adding IAB to a conventional risk model for AF might improve the accuracy of personalized AF prognosis; (4) found clinically relevant differences in long-term absolute risks of AF and ischemic stroke associated with IAB in several subgroups; and (5) found that adding IAB to a conventional risk model for ischemic stroke did not improve risk prediction of ischemic stroke on an individual level.

In line with our results, previous prospective studies of the general population (N≈15 000) have also reported an association between advanced IAB (yes/no) and an increased risk of AF and ischemic stroke.[3,4] However; because of a population of >150 000 individuals, we were able to nuance these findings by looking at IAB with 1, 2, or 3 biphasic P-waves in inferior leads. Interestingly, we found a dose-response association between severity of IAB and the risk of AF and ischemic stroke. As evident from Figure S1, the association with AF, ischemic stroke, and conduction disorder were particularly strong for combinations involving a biphasic P-wave in lead II, either isolated or in combination with a biphasic P-wave in lead aVF. As such, there seems to be a gradient of pathogenicity, with a biphasic P-wave in lead III or its combination with a biphasic P-wave in lead aVF (2 biphasic P-waves) being the most prevalent and associated with better prognosis compared with biphasic P-waves involving lead II.

To test whether IAB could improve risk prediction of AF and ischemic stroke on an individual level, we calculated measures of discrimination. This is important to examine because an association between a given parameter and outcome does not necessarily translate into something meaningful for the individual patient.[18] When IAB was added
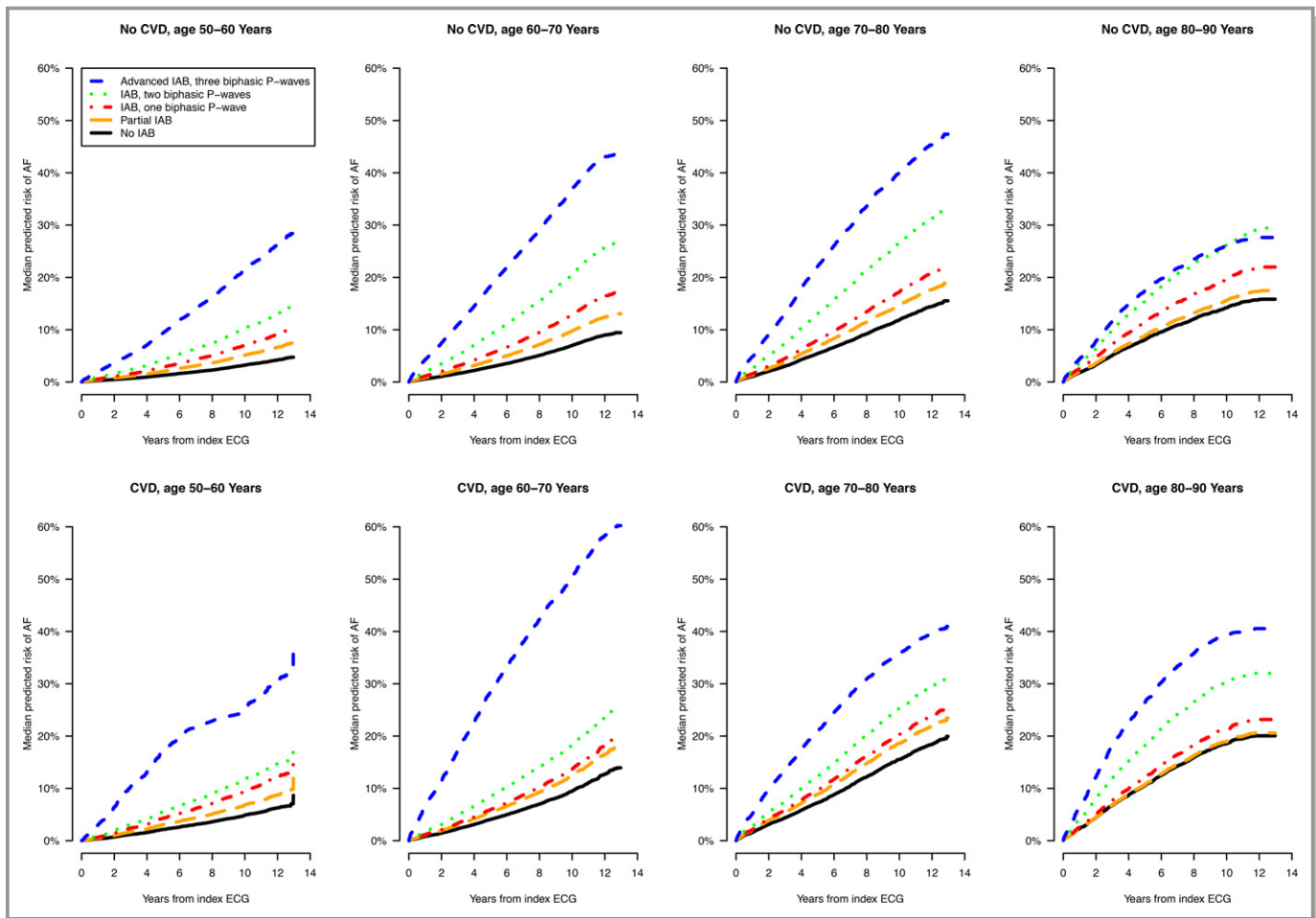
Figure 4. Cumulative incidence curves of interatrial block for the outcome of atrial fibrillation in patients with and without cardiovascular disease at baseline and stratified into 10-year age-groups. Predictions were based on multivariable-adjusted Cox models fitted within the respective age-group and cardiovascular disease group (yes/no). AF indicates atrial fibrillation; CVD, cardiovascular disease; ECG, electrocardiogram; IAB, interatrial block.

to a model containing several well-established risk factors for AF, it significantly improved AUC by ≈1%-point for both individuals with and without CVD at baseline. We believe that such an impact on AUC, although modest, may have clinical implications. In contrast, a recent study found no improvement in *C*-statistics for PR-interval depression, P wave duration, P area, or P terminal force, respectively, when added to a conventional risk model for AF.[19] For ischemic stroke as outcome, no improvement in AUC was observed. As such, IAB does not seem to add anything in risk prediction of ischemic stroke on an individual level. For this reason, we would argue against initiating anticoagulation treatment merely on the presence of IAB, as speculated previously.[4,5]

From a clinical perspective, absolute risks are preferable in comparison to relative risks. As such, we estimated long-term absolute risks of AF and ischemic stroke in different subgroups based on IAB. We have presented these results as cumulative risk taking into account the competing risk of death. This implies that we are presenting the probability of being alive

and developing a condition. When the absolute risk increased most for people at intermediate age compared with older age, it reflects a higher risk of the competing risk of death in the elderly. A total of 50% of the individuals aged 60 to 70 with CVD and advanced IAB (3 biphasic P-waves) developed AF within 10 years of follow-up compared with 10% in those with normal P-wave. Accordingly, the 60- to 70-year-old individual with CVD and advanced IAB seems to be at an increased risk of AF that should not be ignored in clinical practice. Interestingly, patients with IAB and no CVD had a higher risk of AF than patients with hypertension, valvular heart disease, heart failure, and/or ischemic heart disease and no IAB. These data suggest that clinicians may consider monitoring patients with IAB closely for the occurrence of AF, especially for high-risk subgroups. This could be in the form of modern technology, such as different smartphone-dependent devices or other wearables.[20]

We found that IAB on average is associated with larger left atrial end-diastolic volume. However; part of this association
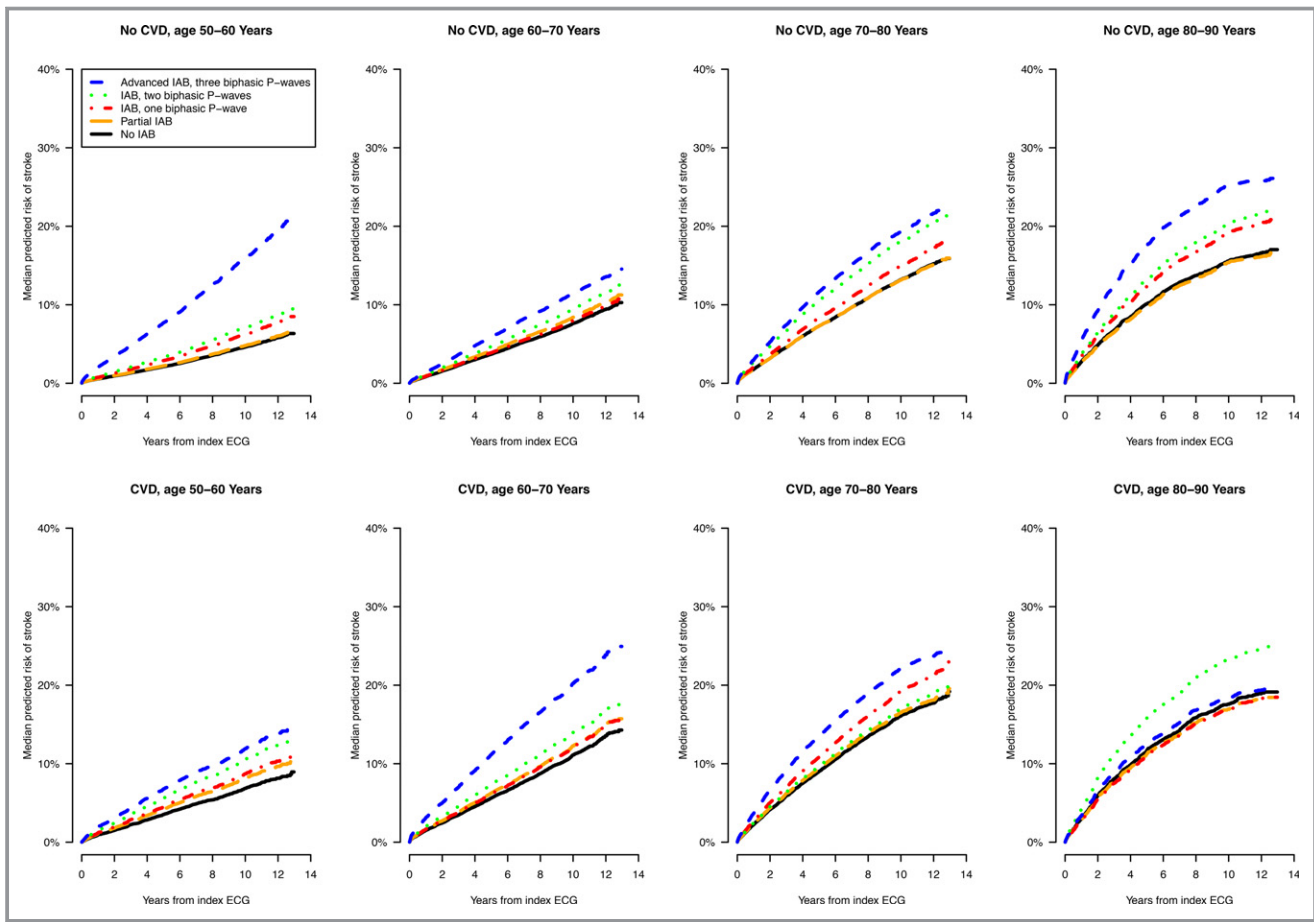
Figure 5. Cumulative incidence curves of interatrial block for the outcome of ischemic stroke in patients with and without cardiovascular disease at baseline and stratified into 10-year age-groups. Predictions were based on multivariable-adjusted Cox models fitted within the respective age-group and cardiovascular disease group (yes/no). CVD indicates cardiovascular disease; ECG, electrocardiogram; IAB, interatrial block.

was driven by higher age in those with advanced IAB compared with those without IAB. Moreover, it is well documented that IAB can exist without evidence of left atrial enlargement.[1] As such, the electrocardiographic IAB is probably a composite of impaired atrial conduction velocity and left atrial enlargement, both contributing to the observed increased risk of AF.[1,21]
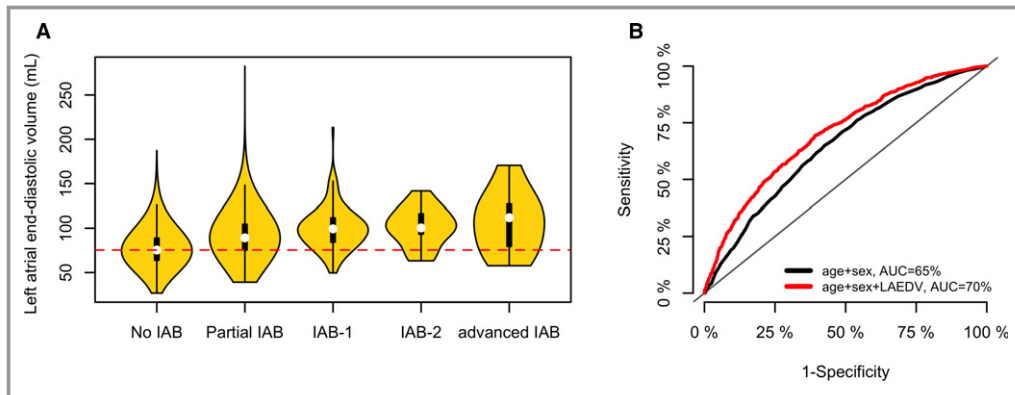
Figure 6. A, Violin plot displaying median, interquartile range, range, and probability density of left atrial end-diastolic volume for normal P-wave and interatrial block. IAB indicates inter-atrial blockIAB-1, interatrial block with one biphasic P-wave in inferior leads; IAB-2, interatrial block with 2 biphasic P-waves in inferior leads. B, Receiving operator curve for the 2 models. In both models, interatrial block (yes/no) is outcome. AUC indicates area under the curve; LAEDV, left atrial end-diastolic volume.

Limitations

Since our study population only included individuals aged 50 to 90 years, we cannot extrapolate the current findings to other age-groups. The reason for excluding individuals <50 years-old was because of statistical power— few individuals <50 years have advanced IAB and events of interests.

The study relied on Danish administrative registries about data on medication use, morbidity and mortality and for some of the entries we do not know the validity. However, a registry-based diagnosis of AF has been found to have a positive predictive value of 93% for electrocardiographically documented AF.[22] High positive predictive values have also been found for our register-based definition of heart failure, ischemic stroke, and hypertension.[10]

Conclusions

In a large primary care population, we found that IAB is associated with increased hazards of AF, ischemic stroke, conduction disorder, and death from all causes. IAB improved risk prediction of AF on an individual level when added to a conventional risk model. For many clinically relevant subgroups, the risk of AF among those with IAB was increased to an extent that could guide clinical decision making. For ischemic stroke as outcome, IAB does not seem to add anything in risk prediction on an individual level.

Sources of Funding

Disclosures

References

1. Bayés de Luna A, Platonov P, Cosio FG, Cygankiewicz I, Pastore C, Baranowski R, Bayés-Genis A, Guindo J, Viñolas X, Garcia-Niebla J, Barbosa R, Stern S, Spodick D. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol*. 2012;45:445–451.

2. Martínez-Sellés M, Baranchuk A, Elosua R, de Luna AB. Rationale and design of the BAYES (Interatrial Block and Yearly Events) registry. *Clin Cardiol*. 2017;40:196–199.

3. O'Neal WT, Zhang Z-M, Loehr LR, Chen LY, Alonso A, Soliman EZ. Electrocardiographic advanced interatrial block and atrial fibrillation risk in the general population. *Am J Cardiol*. 2016;117:1755–1759.

4. O'Neal WT, Kamel H, Zhang Z-M, Chen LY, Alonso A, Soliman EZ. Advanced interatrial block and ischemic stroke: the Atherosclerosis Risk in Communities Study. *Neurology*. 2016;87:352–356.

5. Martínez-Sellés M, García-Izquierdo Jaén E, Fernández Lozano I. Anticoagulation in elderly patients at high risk of atrial fibrillation without documented arrhythmias. *J Geriatr Cardiol*. 2017;14:166–168.

6. Nielsen JB, Graff C, Pietersen A, Lind B, Struijk JJ, Olesen MS, Haunsø S, Gerds TA, Svendsen JH, Køber L, Holst AG. J-shaped association between QTc interval duration and the risk of atrial fibrillation: results from the Copenhagen ECG study. *J Am Coll Cardiol*. 2013;61:2557–2564.

7. GE Healthcare. Marquette™ 12SL™ ECG Analysis Program. Physician's Guide 2036070-006 Revision A, 2010. Available at: http://gehealthcare.com. Accessed April 2, 2012.

8. Nielsen JB, Kühl JT, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, Sinner MF, Bachmann TN, Haunsø S, Nordestgaard BG, Ellinor PT, Svendsen JH, Kofoed KF, Køber L, Holst AG. P-wave duration and the risk of atrial fibrillation: results from the Copenhagen ECG Study. *Heart Rhythm*. 2015;12:1887–1895.

9. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287:2398–2399.

10. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen A-MS, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124.

11. Christiansen MN, Køber L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, Gislason GH, Torp-Pedersen C, Andersson C. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. *Circulation*. 2017;135:1214–1223.

12. Nordestgaard BG, Palmer TM, Benn M, Zacho J, Tybjærg-Hansen A, Smith GD, Timpson NJ. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a mendelian randomisation approach. *PLoS Med*. 2012;9:e1001212.

13. Kühl JT, Lønborg J, Fuchs A, Andersen MJ, Vejlstrup N, Kelbæk H, Engstrøm T, Møller JE, Kofoed KF. Assessment of left atrial volume and function: a comparative study between echocardiography, magnetic resonance imaging and multi slice computed tomography. *Int J Cardiovasc Imaging*. 2012;28:1061–1071.

14. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17:343–346.

15. Benichou J, Gail MH. Estimates of absolute cause-specific risk in cohort studies. *Biometrics*. 1990;46:813–826.

16. Blanche P, Dartigues J-F, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Stat Med*. 2013;32:5381–5397.

17. Gerds TA, Scheike TH, Andersen PK. Absolute risk regression for competing risks: interpretation, link functions, and prediction. *Stat Med*. 2012;31:3921–3930.

18. Wolbers M, Blanche P, Koller MT, Witteman JCM, Gerds TA. Concordance for prognostic models with competing risks. *Biostatistics*. 2014;15:526–539.

19. Magnani JW, Zhu L, Lopez F, Pencina MJ, Agarwal SK, Soliman EZ, Benjamin EJ, Alonso A. P-wave indices and atrial fibrillation: cross-cohort assessments from the Framingham Heart Study (FHS) and Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2015;169:53–61.e1.

20. Olgun Kucuk H, Kucuk U, Yalcin M, Isilak Z. Time to use mobile health devices to diagnose paroxysmal atrial fibrillation. *Int J Cardiol*. 2016;222:1061.

21. Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. *Am Heart J*. 2001;142:823–827.

22. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J*. 2012;46:149–153.

SUPPLEMENTAL MATERIAL

Table S1. Identification of covariates and outcomes.

Conditions	ICD-10 code, procedure, and operation codes
Hypertension	I10, I15
Heart failure	I50
Valvular heart disease	I05, I06, I34, I35 Procedure and operation codes; KFK, KFM
Diabetes Mellitus	E10, E11, E12, E13, E14
Ischemic heart disease	I20, I21, I23, I24, I25, ICD-8: 410
Hyperthyroidism	E05
Obesity	E66
Sleep apnea	G473
Vascular disease	I700, I702-I709, I21, I22
Atrial fibrillation	I48
Ischemic stroke	G458, G459, I63, I64, I74
Conduction disorder	I442, I443, I495

Conduction disorder was a combined endpoint of 3rd degree atrio-ventricular block (I442 and I443) and sick sinus node syndrome (I495). ICD-10=International Classification of Disease, 10th revision.

Table S2. Identification of covariates and outcomes from drugs.

Indication	Drugs (ATC code)
Hypertension	Alpha blockers: C02A, C02B, C02C, Non-loop diuretics: C02L, C02DA, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52, Vasodilaters: C02DB, C02DD, C02DG, C04, C05, Beta-blockers: C07, Calcium blockers: C07F, C08, C09BB, C09DB, ACE-inhibitors: C09
Diabetes	Oral antidiabetics: A10B, Insulin: A10A
Anti-platelets	B01AC
Hyperthyroidism	H03B

Hypertension was defined from discharge diagnosis or as being present if a subject prior to inclusion was treated simultaneously with at least two kinds of antihypertensive drugs. Diabetes and hyperthyroidism were defined from discharge diagnosis or in case of a purchase of prescription medication used for one of the two diseases. ATC=Anatomic Therapeutic Chemical.

Table S3. Lead specific distribution of one and two biphasic P-waves in inferior leads.

IAB_lead	Frequency	Percent
No IAB	113,204	74.1
Partial IAB	24,403	16
One biphasic in II	85	0.06
One biphasic in III	11,363	7.4
One biphasic in aVF	440	.29
Two biphasic in II & III	6	0
Two biphasic in II & aVF	109	0.07
Two biphasic in III & aVF	2,327	1.52
Three biphasic	822	0.54
Total	152,759	100

IAB=inter-atrial block.

Table S4. The hazard of ischemic stroke when censoring for atrial fibrillation during follow-up.

	Hazard ratio (95% CI)	P-value
No IAB	REF	REF
Partial IAB	1.00 (0.96 – 1.05)	0.885
IAB, one biphasic P-wave	1.07 (1.00 – 1.13)	0.052
IAB, two biphasic P-waves	1.17 (1.04 – 1.32)	0.011
Advanced IAB, three biphasic P-waves	1.32 (1.09 – 1.60)	0.005

IAB=inter-atrial block; CI=confidence interval.

Table S5. Examples of Absolute Risk Predictions on an Individual Level.

Patient examples	IAB subgroups	Absolute risk of AF (%) during follow-up from index ECG		
		1 year	5 years	10 years
	No IAB	0.5	2.5	6.1
	Partial IAB	0.7	3.3	8.0
Woman, 65 years of age, no comorbidities, normal heart rate, no ECG sign of left ventricular hypertrophy	IAB, one biphasic P wave	0.9	4.3	10.4
	IAB, two biphasic P waves	1.5	7.0	16.6
	Advanced IAB, three biphasic P waves	2.9	13.2	29.5
	No IAB	0.7	3.3	7.8
	Partial IAB	0.9	4.4	10.4
Man, 65 years of age, no comorbidities, normal heart rate, no ECG sign of left ventricular hypertrophy	IAB, one biphasic P wave	1.2	5.7	13.5
	IAB, two biphasic P waves	2.0	9.2	21.0
	Advanced IAB, three biphasic P waves	3.9	17.2	35.9
	No IAB	0.7	3.7	8.9
	Partial IAB	0.9	4.8	11.3
Woman, 65 years of age, ischemic heart disease, hypertension, normal heart rate, no ECG sign of left ventricular hypertrophy	IAB, one biphasic P wave	1.0	5.2	12.2
	IAB, two biphasic P waves	1.4	7.0	15.9
	Advanced IAB, three biphasic P waves	5.0	23.5	46.3
	No IAB	0.9	4.7	10.8
	Partial IAB	1.2	6.1	13.7
Man, 65 years of age, ischemic heart disease, hypertension, normal heart rate, no ECG sign of left ventricular hypertrophy	IAB, one biphasic P wave	1.3	6.5	14.8
	IAB, two biphasic P waves	1.8	8.7	18.9
	Advanced IAB, three biphasic P waves	6.5	28.5	51.4

Predictions were based on Cox models fitted within the respective age and CVD/no CVD subgroups and adjusted for covariates as described in the manuscript. AF=atrial fibrillation; ECG=electrocardiogram; IAB=inter-atrial block

Figure S1. Multivariable-adjusted hazard ratios for atrial fibrillation, ischemic stroke, conduction disorder, and all-cause mortality by which inferior leads affected by biphasic P-wave. IAB=inter-atrial block; CI_{95}=95% confidence interval.

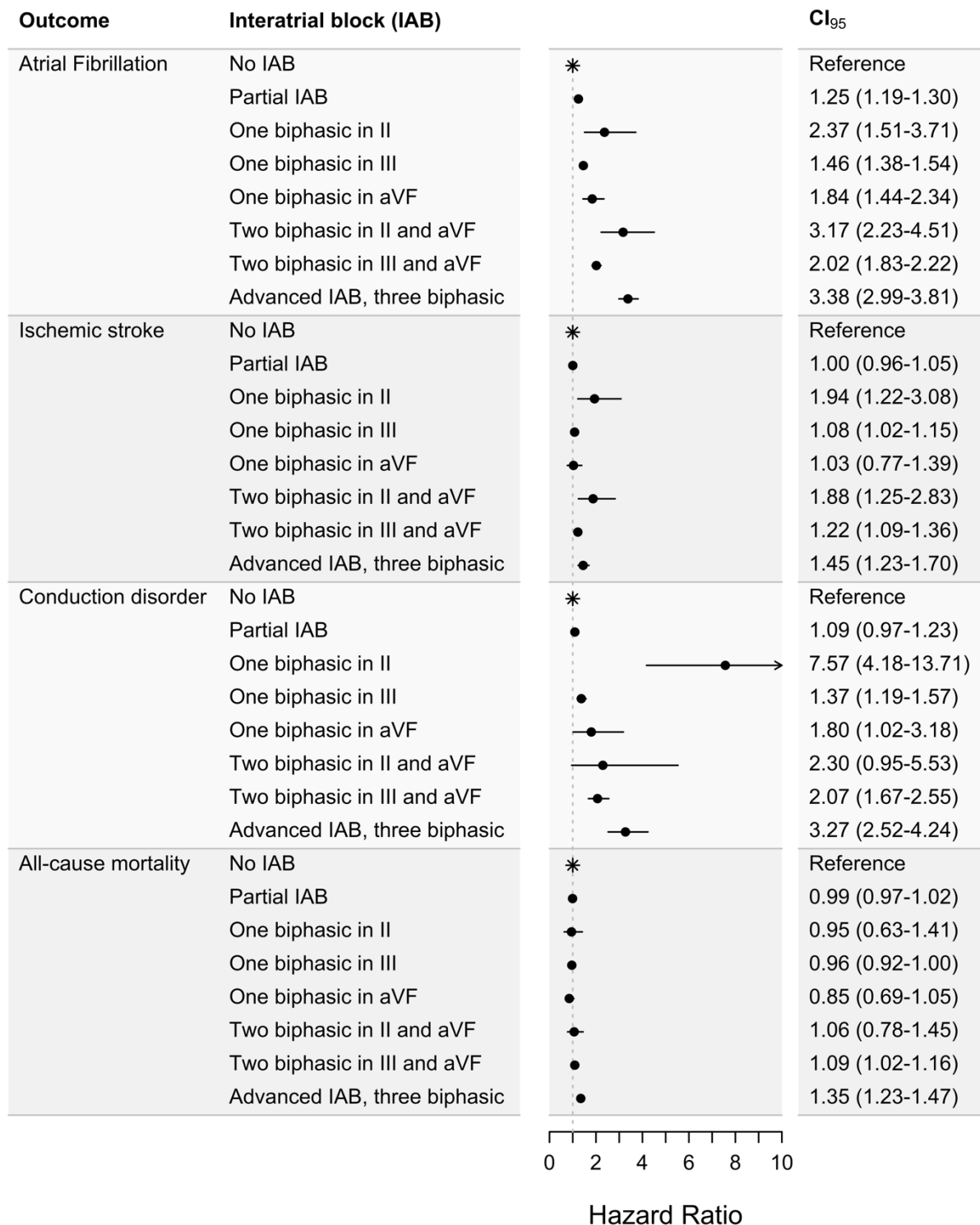| Outcome	Interatrial block (IAB)		CI_{95}
Atrial Fibrillation	No IAB		Reference
	Partial IAB		1.25 (1.19-1.30)
	One biphasic in II		2.37 (1.51-3.71)
	One biphasic in III		1.46 (1.38-1.54)
	One biphasic in aVF		1.84 (1.44-2.34)
	Two biphasic in II and aVF		3.17 (2.23-4.51)
	Two biphasic in III and aVF		2.02 (1.83-2.22)
	Advanced IAB, three biphasic		3.38 (2.99-3.81)
Ischemic stroke	No IAB		Reference
	Partial IAB		1.00 (0.96-1.05)
	One biphasic in II		1.94 (1.22-3.08)
	One biphasic in III		1.08 (1.02-1.15)
	One biphasic in aVF		1.03 (0.77-1.39)
	Two biphasic in II and aVF		1.88 (1.25-2.83)
	Two biphasic in III and aVF		1.22 (1.09-1.36)
	Advanced IAB, three biphasic		1.45 (1.23-1.70)
Conduction disorder	No IAB		Reference
	Partial IAB		1.09 (0.97-1.23)
	One biphasic in II		7.57 (4.18-13.71)
	One biphasic in III		1.37 (1.19-1.57)
	One biphasic in aVF		1.80 (1.02-3.18)
	Two biphasic in II and aVF		2.30 (0.95-5.53)
	Two biphasic in III and aVF		2.07 (1.67-2.55)
	Advanced IAB, three biphasic		3.27 (2.52-4.24)
All-cause mortality	No IAB		Reference
	Partial IAB		0.99 (0.97-1.02)
	One biphasic in II		0.95 (0.63-1.41)
	One biphasic in III		0.96 (0.92-1.00)
	One biphasic in aVF		0.85 (0.69-1.05)
	Two biphasic in II and aVF		1.06 (0.78-1.45)
	Two biphasic in III and aVF		1.09 (1.02-1.16)
	Advanced IAB, three biphasic		1.35 (1.23-1.47)

Hazard Ratio: 0 2 4 6 8 10

Figure S2. Cumulative incidence curves for conduction disorder in patients with and without cardiovascular disease at baseline and stratified into 10-year age-groups. Predictions were based on multivariable-adjusted Cox models fitted within the respective age-group and cardiovascular disease group (yes/no). CVD=cardiovascular disease; ECG=electrocardiogram; IAB=inter-atrial block.