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ORIGINAL RESEARCH

Interatrial Block Detected by a Series of ECGs Before and During Acute Coronary Syndrome Predicts Atrial Fibrillation, Atrial Flutter, and Ischemic Stroke

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BACKGROUND: Interatrial block (IAB) in an ECG, manifesting atrial pathology, is a possible risk factor for atrial arrhythmias and ischemic stroke. IAB is often transiently expressed, posing a major challenge for risk estimation when only a limited number of ECGs are available.

METHODS: This is a retrospective study of 9674 consecutive patients diagnosed with acute coronary syndrome (ACS) between 2007 and 2018. All standard ECGs registered between January 2007 and March 2023 (n=206 668) were digitally stored and analyzed using the General Electric Marquette 12SL algorithm for the presence of an IAB, atrial fibrillation, and atrial flutter. The population was stratified by the extent of the IAB, and patients without an IAB served as controls. Clinical phenotype data and end point data for ischemic stroke were collected by a full disclosure review of hospital records and death certificate data including written accounts of deaths.

RESULTS: The prevalence of an advanced IAB was 8.5% if all previous ECGs, including those recorded during ACS, were screened, whereas it was only 2.4% during ACS. The risk of atrial fibrillation/atrial flutter after ACS increased with the severity of the IAB, and the highest risk was attributable to advanced IAB (age- and sex-adjusted hazard ratio [HR], 2.87 [95% CI, 2.48–3.32]; *P*<0.00001; and fully risk-factor adjusted [including left ventricular ejection fraction] HR, 2.22 [95% CI, 1.89–2.62]; *P*<0.00001). Advanced IAB was also associated with an almost 2-fold risk of ischemic stroke if adjusted for the CHA_2DS_2-VASc score (HR, 1.95 [95% CI, 1.47–2.58]; *P*<0.00001).

CONCLUSIONS: Automatic detection of an IAB from serial ECGs reveals a strong association between atrial pathology and the risk of atrial fibrillation, atrial flutter, and ischemic stroke in patients with ACS.

Key Words: atrial fibrillation ■ atrial flutter ■ interatrial block ■ ischemic stroke

An interatrial block (IAB) detected in an ECG is caused by impaired conduction between the right and left atrium through the Bachmann bundle region.[1] In a partial IAB (pIAB), the electrical impulse is conducted with a delay, and the P-wave duration in the ECG equals or exceeds 120 ms.[2] In an advanced IAB (aIAB), the interatrial conduction through the Bachmann bundle is completely blocked. In addition to a prolonged P-wave duration, the P waves in multiple inferior leads, II, III, and aVF, are biphasic (±) due to left atrial caudocranial activation.

Three general population-based studies, the ARIC (Atherosclerosis Risk in Communities), the Copenhagen ECG Study, and the Finnish Health 2000 Study, have

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CLINICAL PERSPECTIVE

What Is New?

- Interatrial block (IAB) was found to be a significant risk factor for atrial fibrillation and atrial flutter in high-risk cardiac patients treated for acute coronary syndrome, and both partial IAB with 1 biphasic P wave in the inferior leads and advanced IAB were associated with ischemic strokes.
- The risk of these tachyarrhythmias increased with the degree of IAB, and the association was more significant in younger patients. Our findings suggest IAB is a transient phenomenon posing a challenge for risk estimation when only limited records of ECGs are available.

What Are the Clinical Implications?

- These findings could enable better recognition of high-risk patients and help target secondary prevention in the future.

Nonstandard Acronyms and Abbreviations

1 BIF	prolonged P-wave duration and 1 biphasic P wave in inferior leads
12SL	General Electric Marquette 12SL
AFL	atrial flutter
aIAB	advanced interatrial block
IAB	interatrial block
IS	ischemic stroke
LAE	left atrial enlargement
pIAB	partial interatrial block
TOAST	Trial of Org 10172 in Acute Stroke Treatment

demonstrated an association between IAB and incident atrial fibrillation (AF), a finding supported by small studies of patients with coronary artery disease.[3–9] aIAB has also been associated with the incidence of transient ischemic attacks and ischemic stroke (IS).[4,5,10] The higher incidence of AF among patients with IAB could partially explain the increased risk of IS. However, based on the ARIC study, the association was not fully explained by the higher incidence of clinically verified AF.[10] It was suggested that the left atrial pathology and increased thrombogenic factors (atrial cardiomyopathy) together are independent risk factors for IS.[5,10] Thus, IAB could be a beneficial risk marker in identifying patients at a higher risk of IS, and some authors have even proposed anticoagulation therapy for patients with aIAB who are at high thromboembolic risk without a diagnosis of AF.[11]

Despite the promising results, the foremost limitation of IAB as a predictor for AF or IS is the fact that its presentation fluctuates considerably over time, and therefore, the true prevalence can only be assessed by multiple ECG recordings.[3,9,10] The purpose of the present study was to investigate the association between IAB and incident AF, atrial flutter (AFL), and IS in a large cohort of patients with acute coronary syndrome (ACS) (n=9674) with a vast database of >200 000 (n=206 668) ECG recordings, as well as available information on a wide range of cardiovascular risk factors, left ventricular function, and applicable follow-up data for IS.

METHODS

Study Population

The study population was based on 10 314 consecutive patients undergoing invasive evaluation and treatment for ACS in Tampere Heart Hospital (Pirkanmaa region, Finland) between January 1, 2007 and December 31, 2018. ACS served as the baseline for follow-up. If the patient was evaluated for multiple ACS episodes, only the first was recorded. Patients with pacemaker rhythm (n=157), a second- or third-degree atrioventricular block (n=20), and those for whom an ECG had not been recorded within the predefined time limit (7 days before or minimum of 2 months after the angiography date; n=463) were excluded. After exclusions, the population size was 9674.

The patients' data were collected from the Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease (MADDEC) database. This project, launched in 2016, retrospectively combines data from digital electronic databases used in specialized health care and collected from 1990 onward to create a comprehensive study registry focusing on high-risk cardiology patients treated at Tampere Heart Hospital. Tampere Heart Hospital is the sole provider of acute cardiac care in the Pirkanmaa region, Finland, with a catchment population of around 500 000. The database combines electronic health record data with data collected retrospectively by physicians using a full-disclosure review of written health care records and data from the KARDIO database, to which nurses and physicians collect information during the patients' treatment periods. The ECGs of the patients were collected from the electronic database of Fimlab Laboratoriot Oy. Specialized health care and laboratory diagnostics in Finland, including the region of Pirkanmaa, are highly centralized, leading to almost complete coverage for ECG recordings in these patients between 2007 and 2023. Follow-up data for incident AF were collected by analyzing all consecutive ECGs, and follow-up data for incident IS were based on an in-depth review of all patient records, including death certificate data, with no losses to follow-up.[12]

The study design was approved by the scientific monitoring board of Pirkanmaa Hospital District. Due to the retrospective nature of the study, informed consent was not required. The study complies with the Declaration of Helsinki on the ethical principles for medical research. The data that support the findings of this study are available in fully anonymized form for research purposes pending the approval of the study monitoring board.

ECG Data Collection

For ECG feature extraction, all ECGs (n=206 668) of the included patients recorded between the January 1, 2007 and March 15, 2023 were retrieved from a centralized database (the General Electric MUSE system) onto a dedicated study database (median of 17 ECGs per patient, with an interquartile range [IQR] of 9–29 ECGs). The General Electric Marquette 12SL (12SL) algorithm was then used to identify all individual measurable parameters and subsequently derived features, including information on AF and AFL. These parameter data were also used to detect the presence of an IAB and its subtypes.

Definition of IAB and Its Subtypes

The main exposure variables used in our analyses were different IAB subtypes. For this, the population was divided into 4 distinct categories by the severity of the IAB.[4] Patients with a normal P-wave duration (<120 ms) were used as controls. Patients with a prolonged P-wave duration (≥120 ms) and only 1 or no biphasic P waves in the inferior leads (II, III, and aVF) were regarded as having pIAB and divided into 2 groups: patients with only a prolonged P-wave duration and patients with a prolonged P-wave duration and 1 biphasic P wave in inferior leads (1 BIF).[1,2] aIAB was defined as a P-wave duration of ≥120 ms combined with biphasic P waves in at least 2 inferior leads (II, III, and aVF). Biphasic morphology was defined as an amplitude of the initial part of the P wave of ≥20 μV and an amplitude of the terminal part of ≤–20 μV. We chose a cutoff value of 20 μV because changes below this magnitude were not recognized in a reproducible manner on magnified conventional ECG recordings.[13] P-wave durations and the amplitudes of different parts of the P waves were measured automatically. The onset of the QRS complex was defined as an isoelectric line. The P-wave duration was measured from the earliest onset in any lead to the latest offset in any lead. The measurements were made using the 12SL algorithm, which has previously demonstrated excellent agreement with manual interpretation for detecting IAB.[4]

To capture the true prevalence of IAB and its subtypes in our cohort, we searched for all occurrences of IAB in all of the ECGs from the earliest possible date (January 1, 2007) until the index ACS event ECG (baseline). The specific subtype of IAB was defined by the most severe form of IAB detected in all available ECGs. The baseline ECG was defined as the first ECG after angiography (0–60 days). If there was no ECG available from this time frame, the latest ECG recorded up to 7 days prior was used (>95% of the ECGs were recorded on the day of the angiography or the next day). The baseline ECG was also used as the starting point for the follow-up.

We also analyzed the proportion of patients who had left atrial enlargement (LAE) detected by the 12SL algorithm. LAE was defined as prolonged P-wave duration >125 ms and P-wave amplitude >100 μV in lead II or biphasic P wave with amplitude >40 ms and terminal negative portion >40 ms duration and <–100 μV amplitude in lead V1.

End Point Definitions and Adjudication

The primary outcomes were the time to first occurrence of AF, AFL, and IS after an ACS episode.

An incident AF/AFL was defined as a new ECG recording with AF/AFL in the study database as identified by the 12SL algorithm in patients with no AF/AFL in the baseline ECG (n=8831 available for analysis). Incident new-onset AF/AFL was defined similarly but was only analyzed in patients with no history of these arrhythmias (no mentions in written hospital records or the electronic health registry and no previous ECG recordings with AF/AFL) and who were free of AF/AFL at baseline (n=8173 available for analysis). To complement the data for possible cases of AF/AFL occurring before ACS but not covered by the ECG database data, all previous written health records from specialized health care were searched for a mention of AF/AFL, and all electronic health records were searched for previous logs of the equivalent *International Classification of Diseases, Tenth Revision* (*ICD 10*) code I48. The follow-up for incident AF/AFL was available until the March 15, 2023 (or until death if occurring earlier). To verify the accuracy of 12SL algorithm-based AF and AFL detection, all baseline ECG recordings were manually reviewed to evaluate the performance of the 12SL algorithm.

Incident IS events occurring during the follow-up period were identified and adjudicated by trained physicians blinded to IAB status, as described previously in more detail.[12] All patients were followed for this end point regardless of their ECG status at baseline (n=9674 available for analysis). The data collection included an in-depth review of all electronic health records (including laboratory and imaging data and diagnosis codes), all written medical records from specialized health care describing the events and diagnostics, and written death certificates (with *ICD-10* indexed cause of death data). The subtypes of IS were classified by the TOAST (Trial of Org 10 172 in Acute Stroke Treatment) criteria.[13] All incident ISs following ACS were recorded, but only the first was considered in this study. The follow-up data for IS were available until December 31, 2020. The median follow-up time for incident AF/AFL was 7.2 years (IQR, 4.1–10.8 years) and for incident IS 6.2 years (IQR, 3.4–9.5 years).

Statistical Analysis

Multinomial regression analysis was used to analyze factors associated with the prevalence of IAB subtypes. The analysis of the cumulative risk of AF, AFL, or IS was performed using subdistribution hazard analysis, accounting for the competing risk of death due to other causes.

First, an age- and sex-adjusted model was used to study the association of ECG features with the risk of AF/AFL and IS (Model 1). Second, the analyses were adjusted for traditional risk factors, the presence of valvular heart disease, diabetes, and peripheral artery disease, as well as previous coronary interventions (coronary artery bypass grafting and percutaneous coronary interventions), hypertension, hypercholesterolemia, history of stroke, myocardial infarctions, and renal function as demonstrated by the estimated glomerular filtration rate (Model 2). Third, we also considered left ventricle ejection fraction (LVEF) in all analyses (Model 3, data available in 8939 or 92.4% of the population) and additionally the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category)[15] for analysis of association between the exposure variables and the risk of IS. LVEF was measured by the treating cardiologist during the hospitalization after the ACS event by a transthoracic ultrasound. All presented hazard ratios (HRs) are age- and sex-adjusted unless stated otherwise. A *P* value of <0.05 was considered significant. The analyses were performed with SPSS software version 29 (IBM, Armonk, NY) and with R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria), using the packages cmprsk and survival.

RESULTS

The study population consisted of 9674 consecutive patients diagnosed with ACS between January 1, 2007 and December 31, 2018. The mean age was 68.1 years (±11.8 years), and 32.6% (n=3153) of the patients were women. General characteristics of the study population are presented in Table 1.

Table 1. General Characteristics of the Study Population

Age, y, mean±SD	68.1±11.8
eGFR, mL/min per 1.73 m^2, mean±SD	79.1±21.2
Left ventricular ejection fraction, mean±SD	51.4%±11.8
Sex, women	32.6% (3153)
Hypertension	60.4% (5801)
History of stroke	8.0% (778)
History of myocardial infarction	16.5% (1597)
Peripheral artery disease	7.3% (703)
Dyslipidemia	57.7% (5519)
Smoking	
Never	52.5% (4796)
Previous smoker	22.1% (2019)
Active smoker	25.4% (2321)
Previous percutaneous coronary intervention	10.5% (1013)
Previous coronary artery bypass grafting	7.8% (758)
ACS status	
Unstable angina pectoris	17.9% (1736)
Non–ST-segment–elevation myocardial infarction	46.0% (4448)
ST-segment–elevation myocardial infarction	36.1% (3490)
Concomitant valvular heart disease	6.9% (664)
Killip class for heart failure	
Class I (no signs)	78.7% (7597)
Class II (mild congestion)	13.2% (1275)
Class III (heavy congestion)	6.1% (592)
Class IV (cardiogenic shock)	1.9% (183)

Data on smoking status were missing in 5.6% (n=538) of patients, data on left ventricle ejection fraction were missing in 7.6% (n=735) of patients, and data on eGFR, hypertension, peripheral artery disease, dyslipidemia, and Killip class were missing in <5% of patients. ACS indicates acute coronary syndrome; and eGFR, estimated glomerular filtration rate. Values represent %(*n*).

In the baseline ECGs recorded during ACS, the occurrence of any type of IAB was 26.4% (a prolonged P-wave duration was observed in 14.5%, 1 BIF in 9.5%, and aIAB in 2.4% of the patients) (Table 2). When all ECGs recorded before or at baseline were screened, the prevalence of any IAB occurring at least once per patient increased to 55.1%; the prevalence was 23.7% for a prolonged P-wave duration, 22.9% for 1 BIF, and 8.5% for aIAB. Using this subgrouping, patients with IAB were older and had a higher occurrence of significant comorbidities and more recorded ECGs in the database compared with patients with no IAB (Table S1). In multivariable analysis, the most consistent significant risk factors associated with the prevalence of different subtypes of IAB were age, preexisting hypertension, and male sex (Table S2). Furthermore, the number of ECGs recorded before the ACS also remained a significant predictor of observing an IAB in multivariable analyses. Interestingly, ST-segment–elevation myocardial infarction was associated with a lower prevalence of aIAB and 1 BIF (Table S3). There was no statistically

Table 2. Presence of Any Interatrial Block, Partial Interatrial Block, and Advanced Interatrial Block in ECG Recordings During Acute Coronary Syndrome and Before the Index Event

	Value
Occurrence during ACS	
Only prolonged P-wave duration (≥120 ms)	14.5% (1404)
1 BIF (P ≥120 ms and 1 biphasic P wave)	9.5% (917)
Advanced IAB (P ≥120 ms and ≥2 biphasic P waves)	2.4% (234)
No IAB	73.6% (7119)
Occurrence before ACS	
Only prolonged P-wave duration (≥120 ms)	21.8% (2055)
1 BIF (P ≥120 ms and 1 biphasic P wave)	20.5% (1986)
Advanced IAB (P ≥120 ms and ≥2 biphasic P waves)	7.5% (728)
No IAB	50.7% (4905)
Occurrence of new-onset IAB during ACS*	
Only prolonged P-wave duration (≥120 ms)	2.5% (216)
1 BIF (P ≥120 ms and 1 biphasic P wave)	1.0% (90)
Advanced IAB (P ≥120 ms and ≥2 biphasic P waves)	0.3% (26)
Overall occurrence	
Only prolonged P-wave duration (≥120 ms)	23.7% (2288)
1 BIF (P ≥120 ms and 1 biphasic P wave)	22.9% (2213)
Advanced IAB (P≥120 ms and ≥2 biphasic P waves)	8.5% (827)
No IAB	44.9% (4346)

1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; ACS, acute coronary syndrome; and IAB, interatrial block. Values represent %(*n*).

*Patients with no prior ECG before the ACS event were excluded.

significant association between the infarct area and the occurrence of IAB in the acute setting (*P*=0.227), as presented in Table S4.

Based on the results, the LAE was more frequent among patients with IAB: only prolonged P wave (6.2%), 1 BIF (8.5%), and aIAB (8.4%) when compared with patients with no IAB (2.7%) (*P*<0.001). Overall, LAE was present in 5.0% of patients (486/9674) before or at the ACS event.

Evaluation of the Quality of AF and AFL Detection by the 12SL Algorithm

For quality assessment, all ECGs recorded during an ACS episode were verified manually. AF and AFL were verified to be present in 770 (8.0%) and 73 (0.8%) of the ECGs, respectively. The 12SL algorithm showed 99.8% specificity and 91.2% sensitivity for identifying AF and 99.8% specificity and 78.1% sensitivity for identifying AFL in baseline recordings. The corresponding respective positive and negative predictive values were 97.4% and 99.2% for AF and 70.4% and 99.8% for AFL. There were 38 false-positive AFL cases; of these, AF was verified in 60.5% (23/38) of cases, sinus rhythm in 36.8% (14/38) of cases, and junctional rhythm in 2.6% (1/38) of cases.

Association Between IAB and AF/AFL

In our study, 25.3% (n=2447/9674) of the study patients had AF recorded after ACS. All 3 forms of IAB were associated with the risk of AF/AFL (Figure 1): HR, 1.58 (95% CI, 1.40–1.78); *P*<0.00001 for a prolonged P-wave duration; HR, 2.03 (95% CI, 1.8–2.29); *P*<0.00001 for 1 BIF; and HR, 2.87 (95% CI, 2.48–3.32); *P*<0.00001 for aIAB. The results remained similar if the analysis was adjusted for other risk factors besides age and sex (valvular heart disease, diabetes, peripheral artery disease, previous coronary interventions, hypertension, hypercholesterolemia, history of stroke, history of myocardial infarction, estimated glomerular filtration rate, and LVEF). The association between the severity of IAB and AF/AFL was significantly associated with age (*P*<0.0001 for interaction). Demonstrating this, the HR for incident AF/AFL in patients with aIAB was 5.14 among patients aged <65 years (95% CI, 3.42–7.73; *P*<0.00001), whereas the corresponding HR among patients aged ≥65 years was 2.58 (95% CI, 2.21–3.00; *P*<0.00001) (Figure 2). The cumulative incidence rates by age are presented in Figures S1 and S2.The cumulative incidences by IAB category in the entire study population over the course of 12 years' follow-up, along with unadjusted subdistribution hazard estimates, are presented in Figure 3. Analyses were also conducted by adjusting for the number of ECGs recorded, with no significant changes in the results (Table S5). Similar results were also obtained when analyzing the incidence of new-onset AF/AFL. The overall incidence of new-onset AF/AFL after ACS was 1852 cases (22.7% of 8173 patients with no record of AF at baseline). These incidence numbers were associated with an HR of 1.52 (95% CI, 1.34–1.72; *P*<0.00001) for only a prolonged P-wave duration, an HR of 1.89 (95% CI, 1.67–2.14; *P*<0.00001) for 1 BIF; and an HR of 2.55 (95% CI, 2.17–2.99; *P*<0.00001) for aIAB (Figure S3). The association between IAB and incident AFL seemed stronger than between IAB and incident AF, as seen in Figures S4 and S5. LAE, a rarer finding, and did not significantly associate with the risk of AF/AFL (age- and sex-adjusted *P*=0.073).

Association Between IAB and the Risk of IS

aIAB and 1 BIF were statistically significant predictors of IS, with an HR of 1.16 (95% CI, 0.91–1.48; *P*=0.234) for only a prolonged P-wave duration, an HR of 1.34 (95% CI, 1.06–1.70; *P*=0.0131) for 1 BIF, and an HR of 1.98 (95% CI, 1.50–2.61; *P*<0.00001) for aIAB (Figure 4). The results remained similar when adjusted for other risk factors besides age and sex or when adjusted

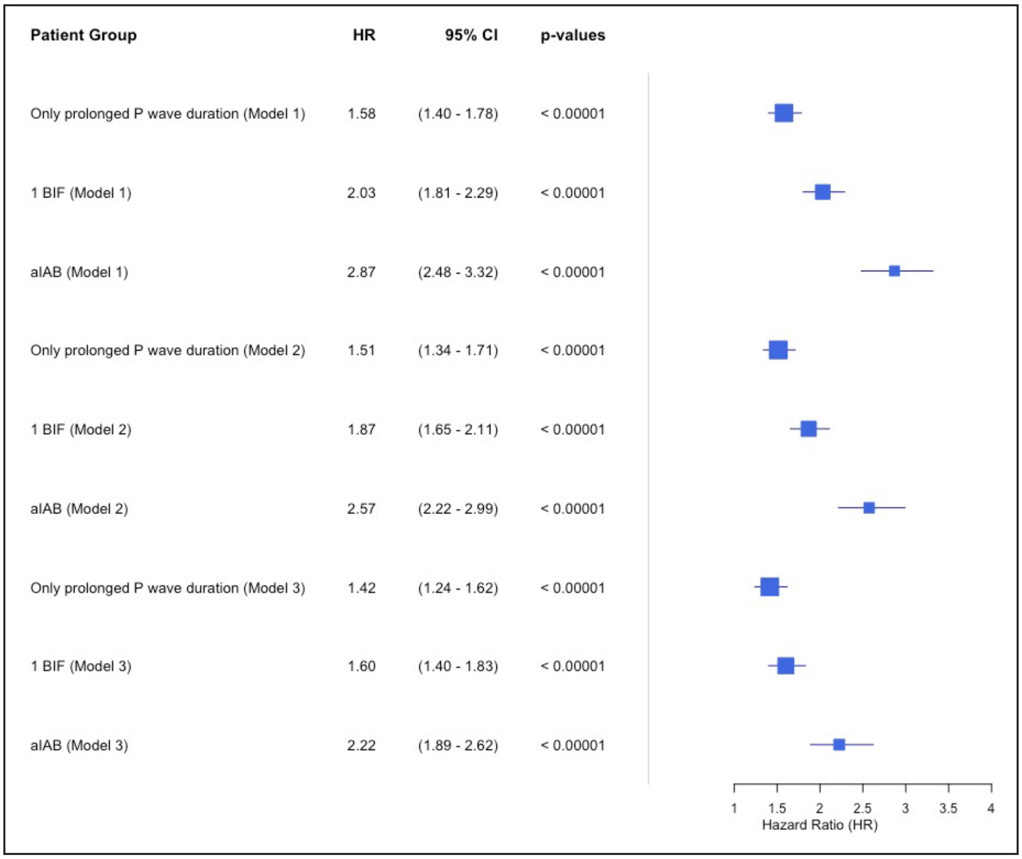

Figure 1. The adjusted risk of incident atrial fibrillation/atrial flutter after acute coronary syndrome by interatrial block category.
Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and risk factors. Model 3: Adjusted for age, sex, risk factors, and left ventricular ejection fraction. 1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; aIAB, advanced interatrial block; and HR, hazard ratio.

for CHA_2DS_2-VASc score information (HR, 1.20 [95% CI, 0.94–1.54]; *P*=0.140 for only a prolonged P-wave duration; HR, 1.35 [95% CI, 1.07–1.71]; *P*=0.0126 for 1 BIF; and HR, 1.95 [95% CI, 1.47–2.58]; *P*<0.00001 for aIAB). The unadjusted cumulative incidence of IS by IAB category over the 12 years of follow-up, along with unadjusted subdistribution hazard estimates, is presented in Figure 5. After adjusting for IAB and other risk factors, LAE was also associated with the risk of IS (HR, 1.68 [95% CI, 1.20–2.35]; *P*=0.0027).

DISCUSSION

The results of this large retrospective study with a high volume of ECG data show that the detection of IAB by using serial ECG recordings yields high-quality information for the risk stratification of AF/AFL and IS.

In general population-based studies, the occurrence of aIAB ranges between 0.5% and 2.1% when only 1 ECG is taken at baseline.[3,4,10] According to our observations, the prevalence of IAB and its subtypes is significantly higher when multiple ECGs are screened as opposed to observing changes in only 1 ECG recording. For example, the prevalence of aIAB, with 2 or 3 biphasic inferior P waves, was 2.4% in ECGs recorded during ACS but increased to 8.5% when all ECGs recorded before the ACS episode were included. Supporting this, in the large general population-based ARIC study, the prevalence of aIAB, with 3 biphasic P waves in the inferior leads, was 0.5% at baseline but increased to 1.3% during follow-up when 3 more ECGs, recorded at 4-year intervals, were considered.[9] In the Finnish Health 2000 Survey (a longitudinal population-based prospective study with 2 ECGs recorded at 10-year intervals), the 1.0% baseline prevalence of aIAB (with 2 or 3 biphasic inferior P waves) increased to 2.0% when both ECGs were considered.[3,5] The third population-based study, the Copenhagen ECG Study,[4] using only 1 ECG recording, found a prevalence of 2.1% for aIAB with ≥2 inferior biphasic leads in patients referred for an ECG recording for various indications, which is close to the single-ECG prevalence in our study (2.4% in ECGs recorded during the ACS episode). In small samples of patients with coronary

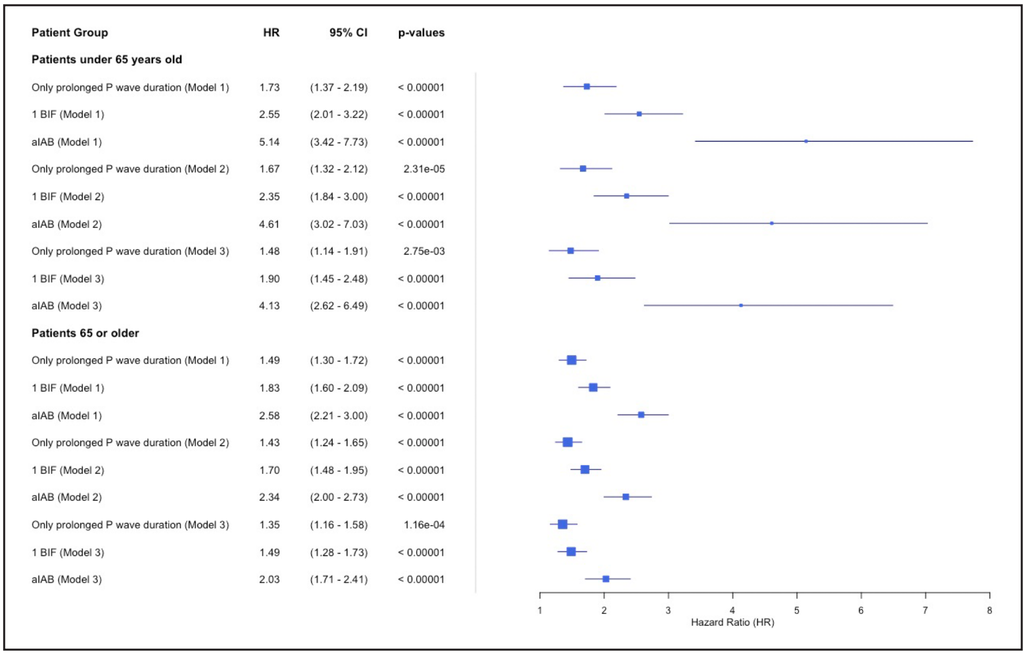

Figure 2. The adjusted risk of incident atrial fibrillation/atrial flutter after acute coronary syndrome by interatrial block category in patients aged <65 years and in patients aged ≥65 years.
Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and risk factors. Model 3: Adjusted for age, sex, risk factors, and left ventricular ejection fraction. 1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; aIAB, advanced interatrial block; and HR, hazard ratio.

or carotid artery disease, even higher prevalences from in-hospital measurements have been reported (3.1%–7.1% for aIAB).[7,8] It has been hypothesized that ischemia in the Bachmann bundle could be a factor explaining the development of IAB in coronary artery disease.[14] However, in our study, the occurrence of IAB was not higher in patients with ST-segment–elevation myocardial infarction. This may be due to the fact that atrial cardiomyopathy is a multifactorial phenomenon, and ischemia is unlikely to increase its incidence in an acute setting. Furthermore, IAB proved to be a labile phenomenon,[3] and it is therefore likely that the true prevalence is higher than previously expected, and IAB can be more accurately captured by leveraging the data from serial ECG recordings over time.

In these population-based studies, aIAB has been associated with AF, with an HR varying from 1.72 to 3.38.[4,5,9] In a small cohort of patients with ST-segment–elevation myocardial infarction, a risk as much as 5-fold higher has been reported.[7] The heterogeneity is probably explained by differences in patient populations and statistical methodologies (in patients with ST-segment–elevation myocardial infarction with high mortality, competing events should be accounted for to avoid inflated estimates) and by the fact that in most studies, the true prevalence of these phenomena is probably not captured due to restricted access to serial ECG data. According to our findings, the age- and sex-adjusted risk of incident AF and AFL was 2.9 times higher in patients who had an aIAB in at least 1 ECG. Similarly, patients with 1 BIF or with only a prolonged P-wave duration also had a notably higher risk of AF (2-fold and 1.6-fold higher risk, respectively, when compared with patients with no IAB). According to our results, the association is also independent of LVEF and other cardiovascular risk factors. Given the ubiquitous nature of IAB (when multiple ECG recordings are screened), this information has clear prognostic implications as well; IAB is an underrecognized risk marker significantly and strongly associated with developing AF/AFL in the future.

Our study confirmed an association, not only between IAB and AF, but also between IAB and incident AFL, which has not, to the best of our knowledge, been reported previously. The hazard estimates between IAB and AFL were similar or greater in magnitude when compared with the association between IAB and AF, with an almost a 4-fold age- and sex-adjusted risk of AFL observed among those with aIAB. The electrophysiological mechanisms of AF and AFL differ from each other, but they are associated with similar clinical settings and can coexist in the same patients.[15] Based on the present study, it cannot be determined whether the association of IAB with AFL reflects right atrial disease or some other mechanism.

Our findings suggest an age-dependent correlation between IAB and AF/AFL. In patients aged

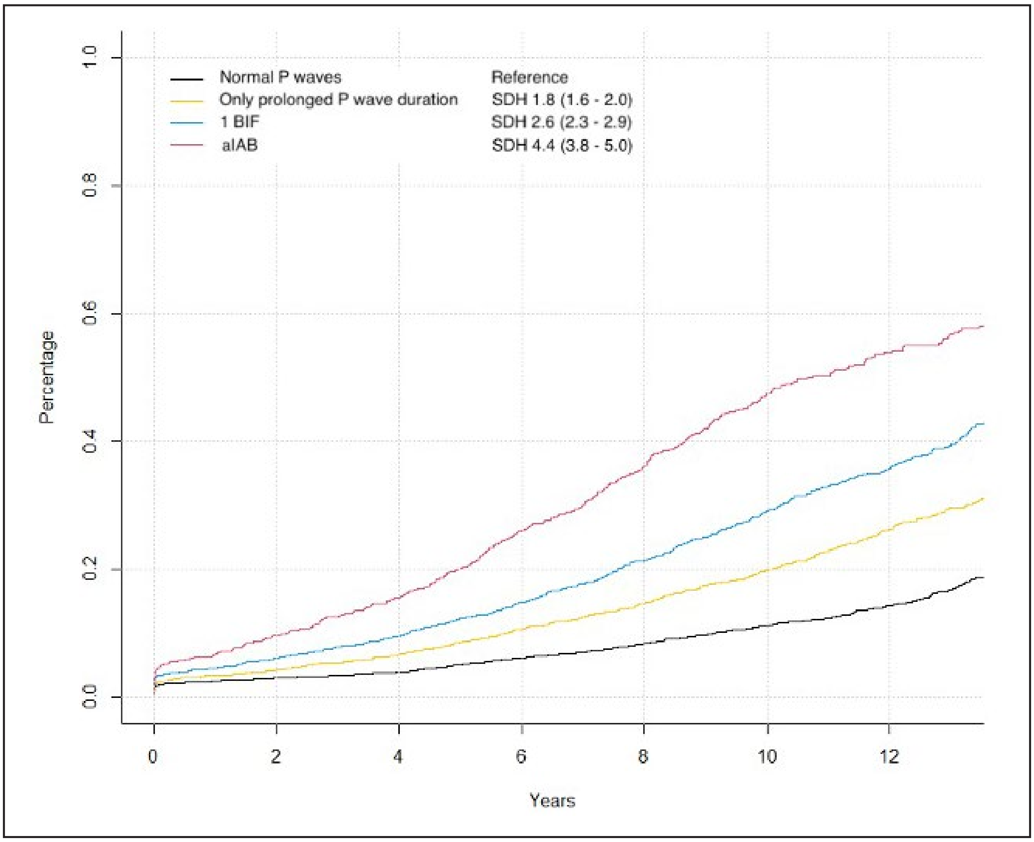

Figure 3. The cumulative incidence of atrial fibrillation/atrial flutter after acute coronary syndrome by interatrial block category.

1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; aIAB, advanced interatrial block; and SDH, subdistribution hazard.

<65 years, the association was significantly stronger than in older patients. This may be because older patients tend to have more comorbidities and other risk factors contributing to the onset of AF. Younger patients tend to suffer lone AF, which is thought to be a manifestation of atrial cardiomyopathy.[16] The younger the patient is, the greater the role that fibrosis and impaired conduction plays in the development of the arrhythmia. Considering patients aged <65 years, we also observed that >45% of those with an IAB developed AF or AFL during the first 10 years of follow-up, whereas the corresponding percentage was only 5% among patients with no IAB.

We also detected a significant association between aIAB and IS. In the population-level ARIC study and in the Copenhagen ECG Study, aIAB was associated with IS by a 1.45- to 1.65-fold higher risk.[4,10] The risk of IS in our cohort was 1.9 to 2.0 times higher for aIAB and 1.3 times higher for 1 BIF, even after adjusting for other cardiovascular risk factors (including AF/AFL at baseline) or for the CHA_2DS_2-VASc score, and accounting for competing events due to high mortality. Only an isolated prolonged P-wave duration with no biphasic inferior P waves did not associate significantly with the risk of IS. The association between aIAB (and pIAB) and IS is also independent of LVEF.

According to our findings and those of others, aIAB is an independent risk factor for IS regardless of AF.[5,10] These findings are thought to be due to atrial cardiomyopathy. aIAB is associated with suboptimal electrical atrioventricular coupling, leading to ineffective atrial contraction and reduced ventricular end-diastolic filling.[17] Interatrial dyssynchrony is a trigger of atrial failure, heart failure, and an activated thrombogenic cascade. Atrial structural abnormalities are thrombogenic, and therefore, factors other than rhythm are responsible for thrombus migration.[18]

In our study, aIAB was a more significant risk factor than pIAB for AF/AFL and IS. This might be due to more extensive atrial cardiomyopathy. Supporting this we also observed that LAE is associated with IS risk. Additionally, aIAB develops more rapidly in patients with pIAB than in patients with a normal P wave.[14] It has been suggested that impaired interatrial conduction due to progressive atrial cardiomyopathy would lead to the development of aIAB. Left atrial disease leads to atrial fibrosis, which correlates with both the persistence and prevalence of AF.[16] On the other hand,

Patient Group	HR	95% CI	p-values
Only prolonged P wave duration (Model 1)	1.16	(0.91 - 1.48)	0.234
1 BIF (Model 1)	1.34	(1.06 - 1.70)	0.0131
aIAB (Model 1)	1.98	(1.50 - 2.61)	< 0.00001
Only prolonged P wave duration (Model 2)	1.20	(0.94 - 1.53)	0.150
1 BIF (Model 2)	1.37	(1.08 - 1.74)	0.0107
aIAB (Model 2)	1.97	(1.48 - 2.63)	< 0.00001
Only prolonged P wave duration (Model 3)	1.20	(0.93 - 1.54)	0.154
1 BIF (Model 3)	1.30	(1.02 - 1.66)	0.0367
aIAB (Model 3)	1.88	(1.40 - 2.53)	2.72e-05
Only prolonged P wave duration (Model 4)	1.20	(0.94 - 1.54)	0.140
1 BIF (Model 4)	1.35	(1.07 - 1.71)	0.0126
aIAB (Model 4)	1.95	(1.47 - 2.58)	< 0.00001

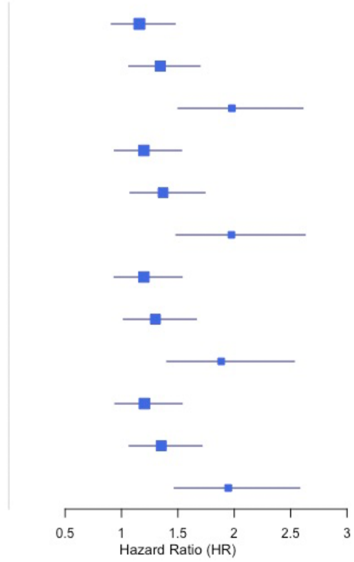

Figure 4. Risk of ischemic stroke after acute coronary syndrome by interatrial block category.
Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and risk factors. Model 3: Adjusted for age, sex, risk factors, and left ventricular ejection fraction. Model 4: Adjusted for age, sex, risk factors, left ventricular ejection fraction, and CHA_2DS_2-VASc score information. 1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; aIAB, advanced interatrial block; and HR, hazard ratio.

AF itself generates atrial remodeling and can contribute to the development of IAB.[19]

The clinical potential of detecting IAB lies in the recognition of patients at a high risk of AF and IS and the possible prevention of these diseases. However, tools for implementing this in clinical practice are still lacking. The recent ARCADIA (Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy) randomized clinical trial in patients with cryptogenic stroke and atrial cardiomyopathy failed to show a benefit of anticoagulation therapy over aspirin.[20] However, the criteria for atrial cardiomyopathy did not include aIAB. Similarly, the results of the use of novel anticoagulants in patients with short subclinical atrial tachyarrhythmias captured by loop recorders or pacemakers have yielded conflicting evidence, highlighting the need for better risk stratification on IS.[21,22] Our findings could enable a better recognition of and subsequently improved secondary prevention in this patient group in the future.

In general, AF episodes may be short and asymptomatic, so it is likely that not all atrial tachyarrhythmia episodes are recorded. IAB is also a partially reversible phenomenon for yet unknown reasons, and it is therefore possible that some patients with IAB were not identified, even in our study using a large database of serial ECGs. However, due to the centralized nature of Finnish health care, we had access to practically all of the ECGs obtained from patients during the follow-up period. We were also able to search through the patients' previous medical records to find mentions of AF and AFL. Furthermore, Tampere University Hospital is the only specialized health care unit treating strokes in the Pirkanmaa region, and we had full access to all death certificate data, including descriptions of the event; thereby, it is unlikely that any clinically significant ISs were missed.[12]

One limitation of the present study is that we used the automatic detection by the 12SL algorithm software for incident AF/AFL in ECG recordings during follow-up. Given the vast body of ECG data, manual revision of all of the ECGs by clinicians was not feasible. However, for the purposes of quality control, almost 10000 baseline ECGs were reviewed manually. Based on the quality metrics, combined with a high number of ECGs recorded from patients, we consider the 12SL algorithm to be a reliable tool for monitoring arrhythmias. Furthermore, the overall sensitivity of automatic detection of these arrhythmias for any given patient likely increases with the number of samples that are available for detection. In our data set, the median number of ECGs recorded after the ACS event was 11 (IQR, 4–20).

CONCLUSIONS

Our findings based on a large retrospective database of serial ECG recordings of patients with ACS demonstrate that both a partial and an advanced IAB have a high true

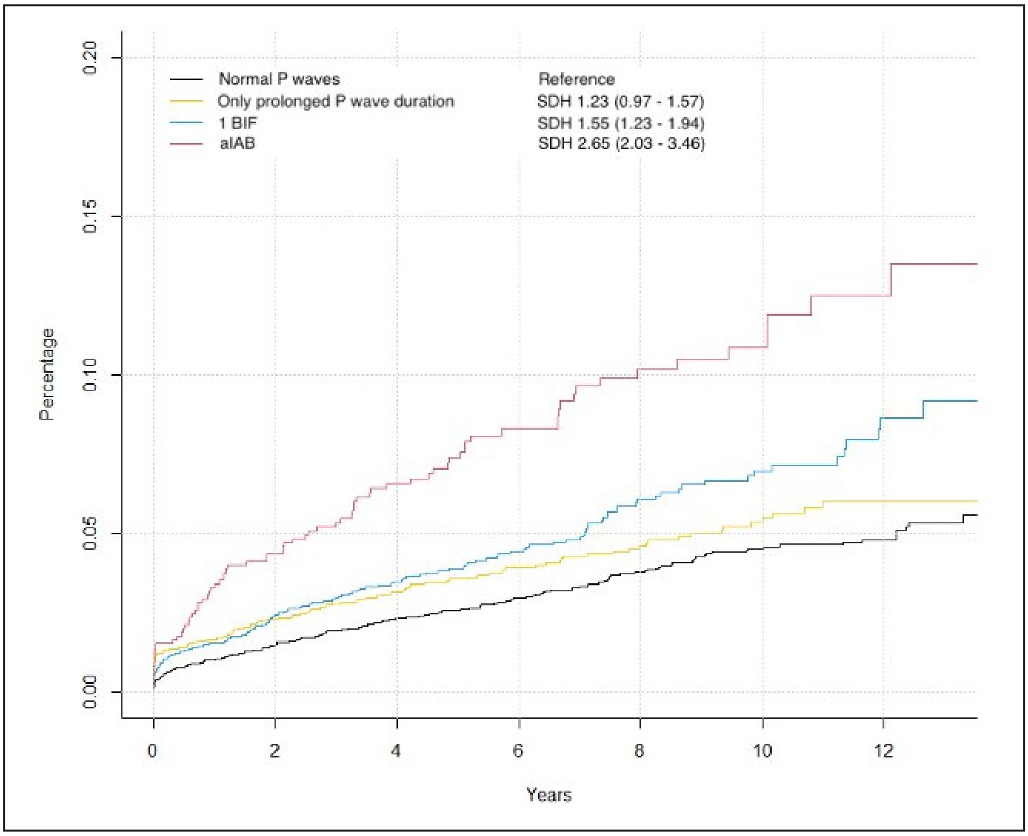

Figure 5. The cumulative risk of ischemic stroke after acute coronary syndrome by interatrial block category.
1 BIF indicates prolonged P-wave duration and 1 biphasic P wave in inferior leads; aIAB, advanced interatrial block; and HR, hazard ratio.

prevalence when screened using serial ECG recordings. These ECG manifestations are significant predictors of AF/AFL, especially in younger patients. Furthermore, aIAB and pIAB with 1 biphasic inferior lead are independent risk factors for IS in patients with ACS. These findings could enable better recognition of high-risk patients and improved secondary prevention in the future.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S5

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