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Predictors of New-onset Atrial Fibrillation in the Setting of Acute Coronary Syndromes - A Nationwide Observational Study

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Abstract

Background: New-onset atrial fibrillation (AF) following acute myocardial infarction (AMI) is associated with adverse outcomes. Studies exploring predictors of AF within the full spectrum of acute coronary syndromes (ACS) are scarce and have yielded conflicting findings. This study aims to identify predictors of new-onset AF in the setting of ACS.

Methods: Patients admitted to 43 Australian hospitals from 2009-2018 with ACS without history of AF were included. Independent clinical and angiographic predictors and the contribution of in-hospital coronary artery bypass grafting (CABG) towards new-onset AF were determined using multivariable logistic regression and mediation analyses.

Results: Of 10,019 consecutive patients admitted with ACS, 806 (8.0%) patients (median age 72 years, 70.8% male) developed new-onset AF. Independent associations with new-onset AF included: older age (adjusted odds ratio [aOR] 1.05, 95% confidence interval [CI] 1.04-1.06), male sex (aOR 1.30, 95%CI 1.04-1.62), higher admission heart rate (aOR 1.02, 95%CI 1.02-1.03), cardiac arrest on admission (aOR 1.89 , 95%CI 1.29-2.77), Killip classes 2 (aOR 1.50, 95%CI 1.21-1.85) and 3/4 (aOR 1.50, 95%CI 1.06-2.13) versus 1, pre-hospital betablocker (aOR 1.32, 95%CI 1.07-1.63) and pre-hospital statin use

(aOR 0.79, 95%CI 0.67-0.93). Among 8370 (85%) of patients who underwent angiography, the presence and extent of coronary disease were additional independent predictors of new-onset AF, mediated predominantly by in-hospital CABG ($p < 0.05$).

Conclusions: Our study identified clinical predictors of new-onset AF in ACS patients. Such patients could be targeted for increased AF surveillance and related adverse outcomes.

Keywords: Atrial Fibrillation; Acute Coronary Syndrome; Clinical; Angiographic; Predictors

Introduction

Acute myocardial infarction (AMI) is a well-established risk factor for incident atrial fibrillation (AF) [1,2]. AF is known to complicate the course of an AMI in 6 – 21% of hospitalized patients [3] and new-onset AF in the setting of an acute MI is associated with adverse in-hospital and long-term outcomes [4,5]. Identifying characteristics of patients who develop AF in the context of acute coronary syndrome (ACS) could inform which patients may need more monitoring or preventative management and is therefore a clinical priority [6]. Standard cardiovascular risk factors and coexistent comorbidities have been reported to be associated with incident AF, however these associations have been inconsistent and vary in different clinical settings [2,7].

There is some evidence that upstream therapy with non-antiarrhythmic drugs that modify the atrial substrate or target specific mechanisms of AF may improve rhythm control and prognosis in AF patients [7]. Such agents include angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), statins, and n-3 polyunsaturated fatty acids [8]. However, for each of these drugs, inconsistent associations in the setting of ACS have been reported [8-14]. While conventional rate and rhythm control and anticoagulation strategies for the management of AF are well-substantiated with evidence-based guidelines, the use of upstream therapy remains controversial and warrants greater clinical attention.

Atrial ischemia and/or infarction has been shown in animal studies to predispose to AF [15-17]. However, studies exploring the relationship between angiographic characteristics such as the extent and location of disease and the development of AF have yielded conflicting findings, with some showing specific disease locations [18-20] and disease burden [21] to be independent predictors for the development of AF after MI while others did not [6, 22]. These studies were frequently confounded by failure to adjust for in-hospital CABG which is itself associated with an approximately 30% incidence of AF [23-25].

Given these uncertainties, we performed an analysis of data obtained from a prospective national multi-centre observational registry to identify contemporary clinical, angiographic and pre-presentation treatment characteristics of patients who developed AF during their ACS. Our aim was to identify at-risk patients of new-onset AF during ACS for whom prioritization of additional observations and preventative measures would be particularly beneficial.

Material and Methods

We undertook an analysis of data obtained from the CONCORDANCE (Cooperative National Registry of Acute Coronary care, Guideline Adherence and Clinical Events) registry which recruited patients from 43 sites around Australia from 2009-2018 [26].

Data Collection

The CONCORDANCE registry enrolled patients with an ACS defined as unstable angina, non-ST-elevation myocardial infarction and ST-elevation myocardial infarction. Patients with ACS events precipitated by non-cardiovascular comorbid conditions such as anaemia or trauma (Type 2 AMI) were excluded. Data were extracted from the medical records by trained study coordinators and included baseline demographic and clinical characteristics, in-hospital investigations, management and outcomes.

Patient Population

Patients admitted with ACS with no previous history of AF constituted our primary cohort. Additional analyses were performed on the subset of these patients who underwent coronary angiography during their index admission in order to evaluate the additional independent contribution of location, burden of coronary disease and performance of in-hospital CABG on the likelihood of new-onset AF.

The CONCORDANCE registry was approved by the research and ethics committees at all participating sites. The analysis was approved by the Sydney Local Health District Human Research Ethics Committee (reference number: HREC/08/CRGH/180).

Definitions and Outcomes

New-onset AF in the primary cohort was defined as new AF detected on index electrocardiograph (ECG) and/or documented during in-hospital stay. Patients with past history of paroxysmal, persistent or permanent AF documented in the medical record were excluded from this study.

Statistical Analysis

Categorical data were summarised as number and percentage: Rao-Scott chi-square test or Fisher's exact test was used to test for differences between the groups. Rao-Scott chi-square test was used to account for the clustering effect of the hospitals. Normally distributed continuous data were summarised as mean and standard deviation (SD) and unadjusted regression analysis was performed within the framework of a generalized estimating equation (GEE) model to compare the groups. GEE was used to correct any bias in the estimates due to clustering effects of hospitals. Skewed continuous data were summarised as median and interquartile interval (IQI) and Wilcoxon rank-sum test was used to assess for differences.

To identify independent predictors of new-onset AF in the setting of ACS, a series of multivariable logistic regression analyses were performed within the framework of GEE to report adjusted odds ratio (aOR) and corresponding 95% confidence interval (CI). The forward fitting procedure was used to build the model. The first step was to build a model with baseline clinical characteristics including upstream medications to explore the association between clinical characteristics and new-onset AF. The clinical characteristics included in the model were chosen based on the statistical significance from the univariable analysis ($p<0.05$) and clinical significance. To avoid potential multicollinearity, we ensured each variable entered into the multivariable models had a Variance Inflation Factor of <2.5.

To examine the angiographic predictors of new-onset AF, we restricted the analyses to the cohort who had undergone coronary angiography. Independent models were developed for the outcomes of i) New-onset AF on admission ECG, and ii) New-onset in-hospital AF (without AF on admission ECG). Clinical characteristics were included in the models as described above with the addition of angiographic characteristics, specifically either disease location or disease burden. Disease location was defined as ≥50% stenosis of one or a combination of cardiac vessels: left main artery, LAD (left anterior descending artery), RCA (right coronary artery) and LCX (left circumflex artery). Disease burden was defined as minor disease, single vessel disease, double vessel disease and triple vessel disease. The in-hospital procedural variable CABG was included in the models predicting new-onset in-hospital AF. To explore the relationship between CABG and disease location and disease burden, sensitivity analyses were performed by including an interaction term between CABG and disease location or CABG and disease burden. Further causal mediation analyses were performed to assess if CABG was a mediator between disease location / burden and new-onset in-hospital AF. The confounders adjusted in the mediation models were the covariates adjusted for in the logistic GEE regression model. The total effect, average causal mediated effect, the average direct effect and the proportion of mediation were estimated, and the corresponding 95% confidence intervals (CI) were obtained using bootstrapping (1000 resamples). In an additional sensitivity analysis, patients who underwent CABG were removed from the cohort of patients with angiographic data and the multivariable analysis predicting all 'new-onset AF' performed. The goodness of fit criteria, including the QIC (goodness of fit statistic for GEE models) and the C-statistic with a 95% confidence interval, were considered in each step of the model building

procedure.

All statistical tests were 2-tailed with the significance level set at 0.05. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA), SPSS version 29.0 (IBM, USA), R version 4.3.2 and mediation R package version mediation_4.5.0.

Results

The details of the study cohort derivation are summarized in the flow chart (Figure 1). Over the 10-year period, 11 146 patients were admitted with ACS. Of these, 10 019 patients had no previous history of AF and constituted the primary study cohort.

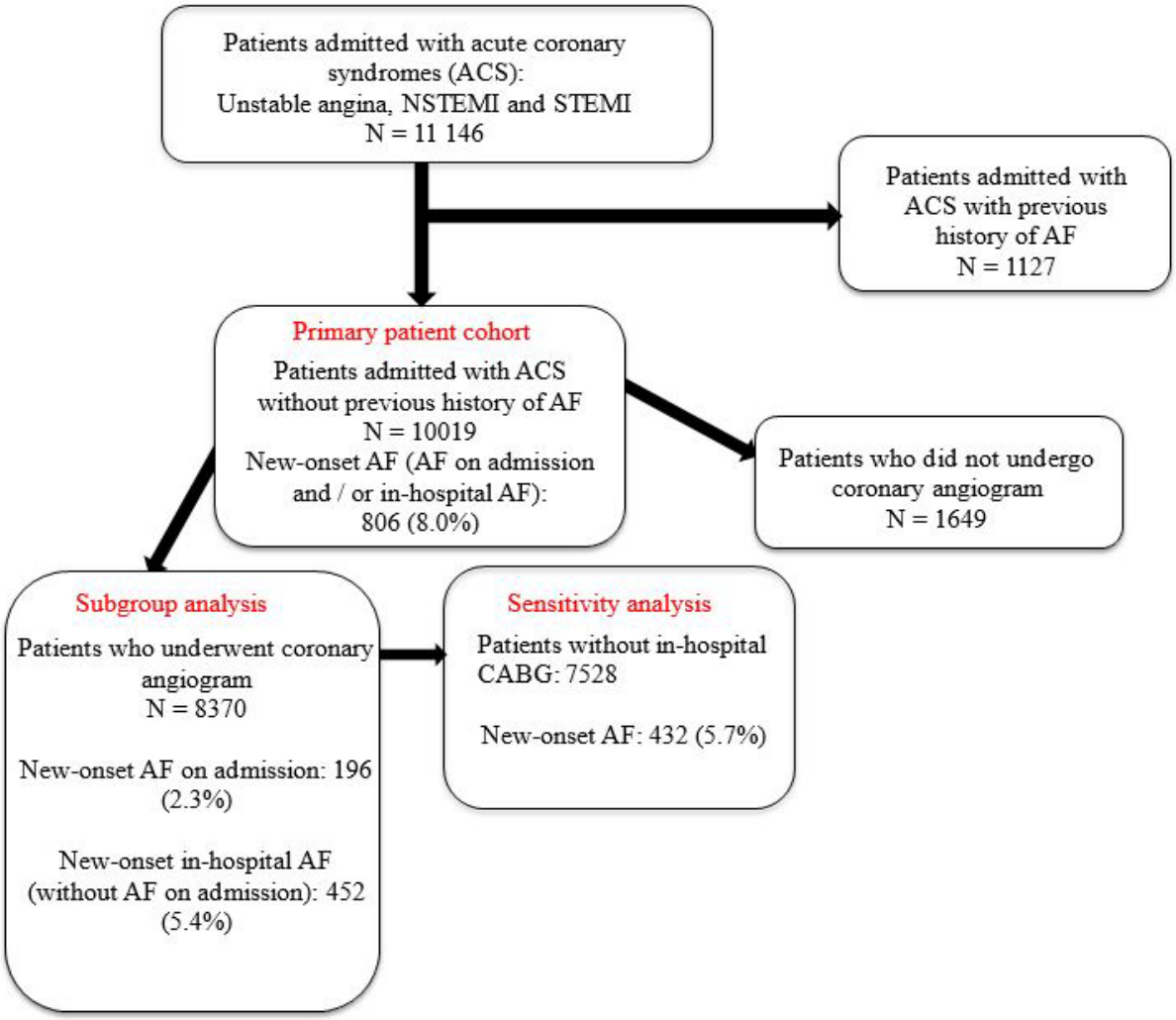

Figure 1: Study flow chart of patients admitted with acute coronary syndromes (ACS)

Legend: ACS: Acute coronary syndrome; CABG: Coronary artery bypass graft surgery; AF: Atrial fibrillation

Baseline Characteristics of Primary Patient Cohort

The baseline clinical characteristics and pre-hospital medications of the primary patient cohort stratified by no AF and new-onset AF are shown in Tables 1 and 2 respectively. Of 10 019 patients, 806 (8.0%) developed new-onset AF. Patients who had new-onset AF were older, had higher heart rate on admission and higher Killip class. A greater proportion of patients with new-onset AF had hypertension, diabetes, peripheral arterial disease, previous stroke / transient ischemic attack (TIA) and chronic renal failure. Patients with new-onset AF also had a higher GRACE risk score (Table 1). The use of pre-hospital aspirin, beta-blockers and angiotensin receptor blockers was higher in patients with new-onset AF compared to patients without new-onset AF ($p < 0.05$) (Table 2).

Table 1: Baseline characteristics of primary patient cohort

Variable	Statistics/ Levels	New-onset AF n (%) n=806	No new-onset AF n (%) n=9213	Total n (%) n=10019	P-value
Age	n	806	9190	9996	.
	Median (IQR)	72 (64, 79)	63 (54, 72)	64 (54, 73)	<.0001
Sex	Male	571/806 (70.8)	6584/9213 (71.5)	7155/10019 (71.4)	0.7948
Systolic blood pressure (mmHg)	n	799	9167	9966	.
	Median (IQR)	138 (117, 156)	140 (122, 157)	140 (122, 157)	0.0085
Diastolic blood pressure (mmHg)	n	798	9159	9957	.
	Median (IQR)	79 (68, 90)	80 (70, 90)	80 (70, 90)	0.0126
Heart rate (per min)	n	799	9161	9960	.
	Median (IQR)	83 (70, 104)	76 (65, 89)	77 (65, 90)	<.0001
BMI	n	527	6176	6703	.
	Median (IQR)	27.6 (24.5, 31.2)	28 (24.9, 31.9)	27.9 (24.8, 31.8)	0.0332
Diagnosis	STEMI	278/806 (34.5)	2957/9213 (32.1)	3235/10019 (32.3)	<.0001
	NSTEMI	447/806 (55.5)	4506/9213 (48.9)	4953/10019 (49.4)	.
	UA	81/806 (10)	1750/9213 (19)	1831/10019 (18.3)	.
Killip class	1	625/806 (77.5)	8356/9213 (90.7)	8981/10019 (89.6)	<.0001
	2	129/806 (16)	661/9213 (7.2)	790/10019 (7.9)	.
	3 or 4	52/806 (6.5)	196/9213 (2.1)	248/10019 (2.5)	.
Cardiac arrest on admission		57/806 (7.1)	318/9213 (3.5)	375/10019 (3.7)	0.0002
Family history of coronary heart disease		221/806 (27.4)	3153/9213 (34.2)	3374/10019 (33.7)	0.0032
Hypertension		530/804 (65.9)	5493/9199 (59.7)	6023/10003 (60.2)	0.0001
Diabetes		252/806 (31.3)	2485/9213 (27)	2737/10019 (27.3)	0.0033
Dyslipidaemia		446/804 (55.5)	5001/9199 (54.4)	5447/10003 (54.5)	0.5845
Smoking History	Never smoked	324/803 (40.3)	3226/9190 (35.1)	3550/9993 (35.5)	<.0001
	Ex-smoker	308/803 (38.4)	3140/9190 (34.2)	3448/9993 (34.5)	.
	Current smoker	171/803 (21.3)	2824/9190 (30.7)	2995/9993 (30)	.
Peripheral arterial disease		67/806 (8.3)	478/9213 (5.2)	545/10019 (5.4)	<.0001
Prior MI		218/806 (27)	2542/9213 (27.6)	2760/10019 (27.5)	0.7734
Prior heart failure		59/806 (7.3)	506/9213 (5.5)	565/10019 (5.6)	0.0372

Previous stroke/transient ischemic attack		83/806 (10.3)	548/9213 (5.9)	631/10019 (6.3)	<.0001
Previous deep vein thrombosis/PE		29/806 (3.6)	307/9213 (3.3)	336/10019 (3.4)	0.6745
Previous percutaneous coronary intervention		140/806 (17.4)	1853/9213 (20.1)	1993/10019 (19.9)	0.1037
Previous coronary artery bypass graft		83/806 (10.3)	891/9213 (9.7)	974/10019 (9.7)	0.5179
Chronic renal failure		95/806 (11.8)	653/9213 (7.1)	748/10019 (7.5)	<.0001
Previous major bleeding		17/806 (2.1)	141/9213 (1.5)	158/10019 (1.6)	0.1013
Grace Risk Score (Fox)	n	771	8889	9660	.
	Median (IQR)	128.5 (105.8, 148.2)	101.1 (81.2, 122.2)	102.8 (82.7, 124.9)	<.0001
Serum creatinine	n	801	9156	9957	.
	Median (IQR)	92 (75, 114)	83 (70.5, 100)	84 (71, 101)	<.0001
Initial haemoglobin (g/L)	n	794	9037	9831	.
	Median (IQR)	137 (125, 151)	143 (131, 153)	142 (130, 153)	<.0001

Primary patient cohort refers to patients admitted with acute coronary syndrome without previous of AF.

BMI, body mass index; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; MI, myocardial infarction; PE, pulmonary embolism

GRACE risk score is calculated based on age (years), heart rate / pulse (beats /min), systolic BP (mmHg), Creatinine (mg/dL), cardiac arrest on admission, ST segment deviation on ECG, abnormal cardiac enzymes and Killip class.

Table 2: Pre-hospitalisation medications in primary patient cohort

Variable	**New-onset AF n (%) n=806**	**No new-onset AF n (%) n=9213**	**Total n (%) n=10019**	**Test**	**P-value**
Pre-hospital aspirin	345/806 (42.8)	3465/9213 (37.6)	3810/10019 (38)	Rao-Scott	0.0150
Pre-hospital betablocker	266/806 (33)	2372/9213 (25.7)	2638/10019 (26.3)	Rao-Scott	0.0003
Pre-hospital ACEi	210/806 (26.1)	2128/9213 (23.1)	2338/10019 (23.3)	Rao-Scott	0.0603
Pre-hospital ARB	199/806 (24.7)	1964/9213 (21.3)	2163/10019 (21.6)	Rao-Scott	0.0149
Pre-hospital statin	365/806 (45.3)	3908/9213 (42.4)	4273/10019 (42.6)	Rao-Scott	0.1757
Pre-hospital other lipid lowering drug	47/806 (5.8)	599/9213 (6.5)	646/10019 (6.4)	Rao-Scott	0.3841

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

Characteristics of Patients who underwent Coronary Angiography

Of the primary patient cohort, 8370 (84%) underwent coronary angiography (Figure 1). These patients were younger with a lower burden of comorbidities than those who did not undergo angiography (Supplementary Table 1). Among these patients, 648 (7.7%) developed new-onset AF: 196 (2.3%) on admission; 452 (5.4%) in-hospital. The presence of disease in any location was associated with a greater likelihood of new-onset AF than no disease, and among patients with disease, the likelihood of new-onset AF increased with greater burden of disease. Of the 842 patients who underwent CABG, 216 (25.7%) had new-onset AF. Of the 4885 patients who underwent PCI, 268 (5.5%) had new-onset AF.

Clinical Predictors of New-Onset AF in the Primary Patient Cohort

Our analysis of the primary patient cohort identified the following independent predictors of new-onset AF: older age (aOR 1.05, 95%CI 1.04-1.06), male sex (aOR 1.30, 95%CI 1.04-1.62), higher admission heart rate (aOR 1.02, 95%CI 1.02-1.03), cardiac arrest on admission (aOR 1.89, 95%CI 1.29-2.77), Killip classes 2 (aOR 1.50, 95%CI 1.21-1.85) and 3/4 (aOR 1.50, 95%CI 1.06-2.13) versus 1, pre-hospital betablocker (aOR 1.32, 95% CI 1.07 -1.63) and pre-hospital statin use (aOR 0.79, 95%CI 0.67-0.93) (all $p < 0.05$) (Table 3).

Table 3: Primary patient cohort: Independent predictors of new-onset AF (Basic clinical characteristics)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.051 (1.044, 1.059)	<.0001	4941.0576	0.735 (0.717, 0.753)
Sex	M vs F	1.3 (1.042, 1.621)	0.0261	.	
Heart rate (per min)		1.022 (1.018, 1.026)	<.0001	.	
Cardiac arrest on admission	Y vs N	1.894 (1.294, 2.774)	0.0086	.	
Hypertension	Y vs N	0.886 (0.742, 1.059)	0.2007	.	
Diabetes	Y vs N	1.091 (0.924, 1.29)	0.3238	.	
Peripheral arterial disease	Y vs N	1.027 (0.787, 1.341)	0.8443	.	
Previous stroke/transient ischemic attack	Y vs N	1.201 (0.952, 1.514)	0.1554	.	
Chronic renal failure	Y vs N	1.02 (0.761, 1.368)	0.8949	.	
Current smoker	Y vs N	1.021 (0.842, 1.239)	0.8298	.	
Pre-hospital ACE/ARB	Y vs N	1.041 (0.891, 1.216)	0.6146	.	
Pre-hospital betablocker	Y vs N	1.319 (1.069, 1.627)	0.0218	.	
Pre-hospital statin	Y vs N	0.787 (0.665, 0.931)	0.0110	.	
Killip class	2 vs 1	1.495 (1.206, 1.854)	0.0064	.	
	3 or 4 vs 1	1.5 (1.056, 2.132)	.	.	
Serum creatinine		1.001 (0.999, 1.002)	0.4303	.	
Initial haemoglobin (g/L)		1 (0.997, 1.003)	0.8527	.	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic

Clinical and Angiographic Predictors of New-Onset AF in the Angiogram Subgroup

Among patients who underwent coronary angiography, 196 were identified as having new-onset AF on admission, and 452 developed their first episode of AF during the admission.

New-onset AF on admission

Predictive characteristics included age (aOR 1.05, 95%CI 1.04-1.07), higher heart rate on admission (aOR 1.04, 95%CI 1.03-1.05), cardiac arrest on admission (aOR 2.53, 95%CI 1.35-4.72) and hypertension (aOR 0.62, 95%CI 0.48-0.81) (data not shown). After adjustment for these, neither disease location (all $p > 0.1$) nor disease burden ($p = 0.48$) were independently associated with new-onset AF on admission (Supplementary Tables 3 and 4 respectively).

New-onset in-hospital AF

In addition to selected clinical characteristics (age, heart rate, cardiac arrest on admission, pre-hospital betablocker, pre-hospital statin, Killip class), we found that coronary disease location or burden at baseline both independently predicted the likelihood of new-onset in-hospital AF (Supplementary Tables 5 and 6). However, after addition of in-hospital CABG to these models, the associations with disease location and disease burden were no longer significant (all $p > 0.05$) and the performance of in-hospital CABG was strongly predictive of new-onset in-hospital AF (Tables 4 and 5). The interaction between these factors and CABG on the likelihood of this outcome was not significant ($p_{inter}>0.05$ for all, data not shown).

Table 4: Patients who underwent coronary angiogram: Independent predictors of new-onset in-hospital AF (Basic clinical characteristics + Disease location + CABG)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.052 (1.042, 1.063)	<.0001	2832.7009	0.81 (0.789, 0.832)
Sex	M vs F	0.993 (0.731, 1.349)	0.9634	.	
Heart rate (per min)		1.006 (1.001, 1.012)	0.0593	.	
Cardiac arrest on admission	Y vs N	2.336 (1.392, 3.922)	0.0265	.	
Hypertension	Y vs N	1.028 (0.784, 1.348)	0.8404	.	
Diabetes	Y vs N	0.976 (0.79, 1.205)	0.8190	.	
Peripheral arterial disease	Y vs N	1.287 (0.906, 1.827)	0.1863	.	
Previous stroke/transient ischemic attack	Y vs N	1.186 (0.827, 1.7)	0.3776	.	
Chronic renal failure	Y vs N	1.055 (0.672, 1.658)	0.8185	.	
Current smoker	Y vs N	1.085 (0.832, 1.414)	0.5538	.	
Pre-hospital ACE/ARB	Y vs N	0.876 (0.701, 1.094)	0.2610	.	
Pre-hospital betablocker	Y vs N	1.564 (1.214, 2.015)	0.0078	.	
Pre-hospital statin	Y vs N	0.771 (0.588, 1.012)	0.0575	.	
Killip class	2 vs 1	1.675 (1.268, 2.214)	0.0006	.	
	3 or 4 vs 1	2.852 (1.817, 4.475)	.	.	
Serum creatinine		1.001 (0.999, 1.002)	0.4896	.	
Initial haemoglobin (g/L)		0.998 (0.992, 1.004)	0.4888	.	

Cardiac vessel with >=50% stenosis during cath: Left main	Y vs N	1.032 (0.763, 1.395)	0.8400	.	
Cardiac vessel with >=50% stenosis during cath: LAD	Y vs N	1.026 (0.802, 1.312)	0.8390	.	
Cardiac vessel with >=50% stenosis during cath: RCA	Y vs N	1.038 (0.841, 1.281)	0.7276	.	
Cardiac vessel with >=50% stenosis during cath: LCX	Y vs N	0.959 (0.753, 1.221)	0.7365	.	
CABG	Y vs N	9.97 (7.62, 13.045)	<.0001	.	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; CABG, coronary artery bypass graft; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic

Table 5: Patients who underwent coronary angiogram: Independent predictors of new-onset in-hospital AF (Basic clinical characteristics + Disease burden + CABG)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.053 (1.043, 1.063)	<.0001	2823.4413	0.811 (0.79, 0.833)
Sex	M vs F	0.978 (0.721, 1.327)	0.8889	.	
Heart rate (per min)		1.007 (1.001, 1.012)	0.0532	.	
Cardiac arrest on admission	Y vs N	2.307 (1.368, 3.891)	0.0285	.	
Hypertension	Y vs N	1.032 (0.79, 1.349)	0.8163	.	
Diabetes	Y vs N	0.966 (0.786, 1.187)	0.7434	.	
Peripheral arterial disease	Y vs N	1.298 (0.912, 1.848)	0.1753	.	
Previous stroke/transient ischemic attack	Y vs N	1.176 (0.821, 1.683)	0.3986	.	
Chronic renal failure	Y vs N	1.055 (0.673, 1.654)	0.8195	.	
Current smoker	Y vs N	1.088 (0.827, 1.432)	0.5512	.	
Pre-hospital ACE/ARB	Y vs N	0.874 (0.702, 1.088)	0.2465	.	
Pre-hospital betablocker	Y vs N	1.575 (1.227, 2.023)	0.0066	.	
Pre-hospital statin	Y vs N	0.771 (0.591, 1.006)	0.0523	.	
Killip class	2 vs 1	1.663 (1.26, 2.193)	0.0006	.	
	3 or 4 vs 1	2.846 (1.811, 4.473)	.	.	
Serum creatinine		1.001 (0.999, 1.002)	0.5012	.	
Initial haemoglobin (g/L)		0.998 (0.991, 1.004)	0.3993	.	
Disease burden	Single vs minor	1.24 (0.889, 1.728)	0.1233	.	

	Double vs minor	1.478 (1.042, 2.097)	.	.	
	Triple vs minor	1.133 (0.811, 1.584)	.	.	
CABG	Y vs N	10.335 (7.795, 13.703)	<.0001	.	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic

On further analyses, CABG was found to be a dominant mediator of new-onset in-hospital AF among patients with coronary disease. The proportion mediated was substantial across all disease locations ($p<0.05$) and the average causal mediation effects were statistically significant, whereas the average direct effects were minimal and not significant, underscoring the dominance of the mediation pathway through CABG (Supplementary Table 7).

Similarly, CABG significantly mediated the relationship between the extent of coronary disease and new-onset atrial fibrillation. The indirect effect was positive and significant for double and triple vessel diseases. For double vessel disease, nearly half of the effect was mediated by CABG (49.3%) whereas for triple vessel disease, 89.8% was mediated by CABG (both $p < 0.05$) (Supplementary Table 8).

Sensitivity Analyses: Clinical and angiographic predictors of new-onset AF among patients who did not undergo CABG

Sensitivity analyses modelling the outcome of new-onset AF restricted to the 7528 patients who did not undergo CABG showed similar clinical associations to the model based on the full primary patient cohort except for the variable male sex which was not significant. There was no independent association with coronary disease location (all $p > 0.4$ for all) or burden ($p = 0.47$) (Supplementary Tables 9 and 10 respectively).

Discussion

In this contemporary Australian study of over 10,000 patients with ACS, 8.0% of patients developed new-onset AF. In determining the predictors of this rhythm disturbance, our principal findings were 1) well-known baseline high risk clinical features were independently associated with new AF; 2) pre-hospital statin use was associated with a lower likelihood of new-onset AF, while beta-blocker use was associated with a greater likelihood of new-onset AF; 3) both coronary disease location and increased disease burden were associated with a greater likelihood of new-onset in-hospital AF, but this was largely mediated by the greater likelihood of these patients undergoing in-hospital CABG.

Our incidence rate of 8% closely aligns with a recent meta-analysis of 109 studies consisting of 8 239 364 patients that showed 7.3% of patients with ACS had newly diagnosed AF [27]. The independent predictive risk of older age, higher heart rate, higher Killip class and cardiac arrest on admission and new-onset AF is also consistent with previous studies and has generally been attributed to AF being precipitated by the acute haemodynamic stress associated with myocardial ischaemia/infarction in patients with poorer myocardial reserve [19,22,28].

Our finding of pre-hospital statin therapy being associated with a lower risk of new-onset AF concurs with findings from other studies [29-34]. The upregulated inflammatory cascade observed during an ACS has been implicated in the pathophysiology of AF [35] and it has been hypothesised that the anti-inflammatory and anti-oxidative properties of statins exert an antiarrhythmic effect, independent of their lipid-lowering effect [8,36,37]. Interestingly, a meta-analysis of 26 randomised controlled trials showed that PCSK9 monoclonal antibody therapy also reduced the risk of AF in patients with high cardiovascular risk when compared with placebo [38], suggesting lipid lowering effect per se or alternative off-target effects to also play some role.

A number of meta-analyses have shown that renin-angiotensin-aldosterone blocker (ACE-I or ARB) therapy is associated with a modest but statistically significant reduction in AF onset and / or recurrence, in patients with heart failure with systolic dysfunction, but not in patients with coronary artery disease [11-14]. For instance, the meta-analysis by Khatib et al. showed two trials which included post-MI patients (TRACE, GISSI-3) and six trials that enrolled patients with hypertension / at high risk of cardiovascular disease or with documented coronary artery disease (CAPPP, STOP-H2, VALUE, HOPE, LIFE, TRANSCEND) demonstrated no overall statistically significant reduction of new-onset atrial fibrillation[14]. Among the two post-MI trials, the smaller study TRACE (n = 1749) with a longer follow-up of 2 – 4 years, showed that trandolapril treatment significantly reduced the risk of developing atrial fibrillation by 55% in patients with left ventricular systolic dysfunction [39], whereas GISSI-3, the larger study (n = 17 944) with 6 weeks and 6 months follow-up in which 84% of patients had no evidence of heart failure at the time of MI, failed to detect a statistically significant effect [40]. Consistent with these findings, our study found no association between pre-hospital use of ACE-I or ARB and the development of new-onset AF in patients admitted with ACS. This could also be attributed to the fact that majority of patients (89.6%) admitted with ACS in our study cohort were of Killip Class I, without evidence of congestive cardiac failure.

The association between betablocker therapy and increased likelihood of new AF has not been reported before and is counterintuitive, as betablockers have been associated with a lower likelihood of recurrent AF in patients with a past history of the condition [41,42]. This finding may reflect ascertainment bias or residual confounders.

The high rates of angiography in our patient cohort together with detailed data on disease burden and location provided an opportunity to explore the independent contribution of coronary disease to the development of new-onset AF during the acute phase of an ACS. Our predictive models among patients undergoing angiography adjusting for baseline clinical characteristics did indeed find presence of angiographically significant disease to be independently associated with an increased likelihood of new-onset in-hospital AF, and this association became greater as the burden of disease increased. However, more than 30% of our new-onset AF patients underwent CABG in hospital, an operation which is performed for patients with greater burden of coronary disease, which is itself, associated with the development of AF in approximately 30% of cases [24,25]. It therefore was a strong potential confounder and after adding this in-hospital procedural variable to our models for new-onset in-hospital AF, the association with disease location and burden was no longer apparent. Indeed, on mediation analysis, CABG appeared to be the predominant factor accounting for the likelihood of the development of AF among patients with demonstrated coronary disease. Two additional analyses were conducted to explore non-CABG mediated angiographic predictors of new-onset AF. Firstly, we focussed on predictors of new-onset AF that was detected on admission, as this could not have been precipitated by CABG performed later. In this model, we could not demonstrate an association between coronary disease location or burden and new-onset AF on admission. Secondly, we excluded patients who underwent CABG and modelled the outcome of new-onset AF detected at presentation or during admission and once more, we could not find an association between coronary disease location or burden and new-onset AF in this cohort.

Our data are consistent with several studies. In the OACIS observational study (n=2475), angiographic characteristics and patency of the infarct-related artery were not independent predictors of AF [22]. A study by Braga et al. (n=902) demonstrated that new-onset AF was associated with the absence of coronary lesions [6]. In contrast to this, the GUSTO-I clinical trial of STEMI (n=40 891) showed that inferior location of the MI was associated with AF in the setting of ST-elevation MI [19]. Alasady et al. (n=2460) found coronary artery disease affecting the atrial branches was an independent predictor for the development of AF after MI [18] and a study by Shiba et al. (n = 204) found that proximal occlusion in the right coronary artery involving the atrial branch was a strong predictor of new-onset AF after MI [20]. These differences could be explained by differences in study sample size and design. The GUSTO trial was restricted to patients with STEMI and did not include the broader cohort of ACS patients. Importantly, the GUSTO-I trial did not exclude the possibility that the performance of CABG in patients with disease, not the coronary

anatomy per se, was responsible for AF in these patients. Both the studies by Alasady et al. and Shiba et al. were single-center observational studies and the study by Alasady et al did not adjust for basic clinical characteristics. It is noteworthy that we did not find an interaction between CABG vs not and disease presence or location on the occurrence of new-onset in-hospital AF. Therefore, it remains possible that these associations may be present, but our sample size was not sufficient to detect this.

Our findings should be interpreted in the context of a number of potential limitations. Given that our registry did not collect the exact timing of in-hospital AF in relation to other events or procedures such as CABG, we could not determine which patients had AF before or after the events and procedures and this may have led to an over-estimation of the association with CABG. However, we believe our sensitivity and subgroup analyses largely accounted for these limitations. Furthermore, the new AF rate in our in-hospital CABG population was 25.7%, within the range of 25-40% established in the literature [25,43]. Restricting our cohorts in these analyses did reduce the number of AF events which may account the lack of independent contribution of coronary disease location or burden to new-onset AF. The type of AF (paroxysmal, persistent and permanent AF) was also not specified for the patients. As this is an observational study, a degree of selection bias and failure to adjust for unmeasured confounders was unavoidable. For example, we did not collect information on antiarrhythmic therapy other than beta-blockers. Nor could we account for changes in the patients' conditions during admission. The haemodynamic status of patients might change throughout the admission regardless of their baseline treatment, and haemodynamic instability is known to predispose patients to the development of AF [19,28] . In addition, patients might also develop new comorbidities and commence new medications in the hospital admission that increase their risk of developing AF. Our dataset did not capture changes in haemodynamic status as well as changes in all comorbidities and medications throughout the entire admission, hence potentially contributing to residual confounding.

In conclusion, using a prospectively collected national clinical quality registry, we have identified patients with new-onset AF in the setting of ACS. Older patients, those with higher Killip class, higher heart rate and cardiac arrest on admission are at increased risk of new-onset AF when admitted with ACS. The use of pre-hospital statins but not ACE-I or ARB therapy, was associated with a lower risk of new-onset AF in the setting of ACS. In-hospital new-onset AF was largely accounted for by CABG. However, we could not exclude additional contributions from coronary disease burden and location. As patients who develop AF in the setting of ACS have a higher rate of major adverse in--hospital events, they should be targeted for increased surveillance for AF and be monitored for AF-related adverse clinical outcomes during the post-infarct period, so that early intervention and additional post-discharge support can be facilitated. Future studies should include larger patient cohorts, different AF subtypes and the timing of CABG in relation to AF, including a dedicated time-event analysis to clarify this relationship. They should also explore whether early optimisation of medical therapy and the use of other interventions, can prevent the development of new-onset AF and other related adverse outcomes in the setting of ACS.

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Disclosures

The authors have no additional disclosures to report.

Supplementary Material

Supplementary Tables

Supplementary Table 1: Comparison of patients who underwent coronary angiogram versus patients who did not undergo coronary angiogram (Primary patient cohort)

Variable	Statistics/ Levels	Catheterisation n (%) n=8370	No Catheterisation n (%) n=1649	Total n (%) n=10019	Test	P-value
Age	n	8347	1649	9996		.
	Median (IQR)	63 (54, 72)	71 (59, 81)	64 (54, 73)	Wilcox	<.0001
Sex	M	6110/8370 (73)	1045/1649 (63.4)	7155/10019 (71.4)	Rao-Scott	.
Systolic blood pressure (mmHg)	n	8340	1626	9966		.
	Median (IQR)	140 (122, 158)	137 (120, 155)	140 (122, 157)	Wilcox	0.0010
Diastolic blood pressure (mmHg)	n	8333	1624	9957		.
	Median (IQR)	80 (70, 91)	75 (66, 86)	80 (70, 90)	Wilcox	<.0001
Heart rate (per min)	n	8332	1628	9960		.
	Median (IQR)	76 (65, 90)	79 (65, 92)	77 (65, 90)	Wilcox	0.0020
BMI	n	5947	756	6703		.
	Median (IQR)	28 (25, 31.9)	27.4 (24.2, 31.5)	27.9 (24.8, 31.8)	Wilcox	0.0073
Diagnosis	STEMI	3091/8370 (36.9)	144/1649 (8.7)	3235/10019 (32.3)	Rao-Scott	.
	NSTEMI	4204/8370 (50.2)	749/1649 (45.4)	4953/10019 (49.4)	Rao-Scott	.
	UA	1075/8370 (12.8)	756/1649 (45.8)	1831/10019 (18.3)	Rao-Scott	.
Killip class	1	7658/8370 (91.5)	1323/1649 (80.2)	8981/10019 (89.6)	Rao-Scott	<.0001
	2	559/8370 (6.7)	231/1649 (14)	790/10019 (7.9)	Rao-Scott	.
	3 or 4	153/8370 (1.8)	95/1649 (5.8)	248/10019 (2.5)	Rao-Scott	.
Cardiac arrest on admission		297/8370 (3.5)	78/1649 (4.7)	375/10019 (3.7)	Rao-Scott	0.3276

Family history of coronary heart disease		2996/8370 (35.8)	378/1649 (22.9)	3374/10019 (33.7)	Rao-Scott	.
Hypertension		4789/8356 (57.3)	1234/1647 (74.9)	6023/10003 (60.2)	Rao-Scott	<.0001
Diabetes		2127/8370 (25.4)	610/1649 (37)	2737/10019 (27.3)	Rao-Scott	<.0001
Dyslipidaemia		4375/8356 (52.4)	1072/1647 (65.1)	5447/10003 (54.5)	Rao-Scott	<.0001
Smoking History	Never smoked	2827/8350 (33.9)	723/1643 (44)	3550/9993 (35.5)	Rao-Scott	<.0001
	Ex-smoker	2827/8350 (33.9)	621/1643 (37.8)	3448/9993 (34.5)	Rao-Scott	.
	Current smoker	2696/8350 (32.3)	299/1643 (18.2)	2995/9993 (30)	Rao-Scott	.
Peripheral arterial disease		365/8370 (4.4)	180/1649 (10.9)	545/10019 (5.4)	Rao-Scott	<.0001
Prior MI		1905/8370 (22.8)	855/1649 (51.8)	2760/10019 (27.5)	Rao-Scott	.
Prior heart failure		312/8370 (3.7)	253/1649 (15.3)	565/10019 (5.6)	Rao-Scott	<.0001
Previous stroke/transient ischemic attack		433/8370 (5.2)	198/1649 (12)	631/10019 (6.3)	Rao-Scott	<.0001
Previous deep vein thrombosis/PE		236/8370 (2.8)	100/1649 (6.1)	336/10019 (3.4)	Rao-Scott	<.0001
Previous percutaneous coronary intervention		1458/8370 (17.4)	535/1649 (32.4)	1993/10019 (19.9)	Rao-Scott	<.0001
Previous coronary artery bypass graft		610/8370 (7.3)	364/1649 (22.1)	974/10019 (9.7)	Rao-Scott	<.0001
Chronic renal failure		450/8370 (5.4)	298/1649 (18.1)	748/10019 (7.5)	Rao-Scott	.
Previous major bleeding		109/8370 (1.3)	49/1649 (3)	158/10019 (1.6)	Rao-Scott	0.0010
Grace Risk Score (Fox)	n	8121	1539	9660		.
	Median (IQR)	101.7 (82.5, 122.2)	113.4 (84, 140.6)	102.8 (82.7, 124.9)	Wilcox	<.0001

BMI, body mass index; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; MI, myocardial infarction; PE, pulmonary embolism
GRACE risk score is calculated based on age (years), heart rate / pulse (beats /min), systolic BP (mmHg), Creatinine (mg/dL), cardiac arrest on admission, ST segment deviation on ECG, abnormal cardiac enzymes and Killip class.

Subgroup analyses: Patients who underwent coronary angiogram

Supplementary Table 2: Angiographic and hospital revascularisation characteristics of patients who underwent coronary angiogram

Variable	Statistics/ Levels	New-onset AF n (%) n=648	No new-onset AF n (%) n=7722	Total n (%) n=8370	Test	P-value
Left main disease		100/648 (15.4)	461/7722 (6)	561/8370 (6.7)	Rao-Scott	<.0001
LAD disease		443/648 (68.4)	4417/7722 (57.2)	4860/8370 (58.1)	Rao-Scott	<.0001
RCA disease		385/648 (59.4)	3769/7722 (48.8)	4154/8370 (49.6)	Rao-Scott	<.0001
LCx disease		338/648 (52.2)	3015/7722 (39)	3353/8370 (40.1)	Rao-Scott	<.0001
Vein graft disease		18/648 (2.8)	213/7722 (2.8)	231/8370 (2.8)	Rao-Scott	0.9732
IMA disease		9/648 (1.4)	61/7722 (0.8)	70/8370 (0.8)	Rao-Scott	0.1722
Disease burden	Minor	69/648 (10.6)	1193/7722 (15.4)	1262/8370 (15.1)	Rao-Scott	<.0001
	Single	165/648 (25.5)	3037/7722 (39.3)	3202/8370 (38.3)	Rao-Scott	.
	Double	190/648 (29.3)	2020/7722 (26.2)	2210/8370 (26.4)	Rao-Scott	.
	Triple	224/648 (34.6)	1472/7722 (19.1)	1696/8370 (20.3)	Rao-Scott	.
CABG		216/648 (33.3)	626/7722 (8.1)	842/8370 (10.1)	Rao-Scott	<.0001
PCI		268/648 (41.4)	4617/7722 (59.8)	4885/8370 (58.4)	Rao-Scott	<.0001

PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; IMA, internal mammary artery

Supplementary Table 3: Patients who underwent coronary angiogram: Independent predictors of new-onset AF on admission (Basic clinical characteristics + Disease location)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.054 (1.04, 1.068)	0.0001	1597.7458	0.797 (0.764, 0.83)
Sex	M vs F	1.465 (0.971, 2.211)	0.0738	.	
Heart rate (per min)		1.038 (1.031, 1.045)	<.0001	.	
Cardiac arrest on admission	Y vs N	2.514 (1.34, 4.719)	0.0412	.	

Hypertension	Y vs N	0.633 (0.484, 0.827)	0.0021	.	
Diabetes	Y vs N	0.993 (0.69, 1.43)	0.9713	.	
Peripheral arterial disease	Y vs N	0.845 (0.389, 1.837)	0.6635	.	
Previous stroke/transient ischemic attack	Y vs N	1.35 (0.832, 2.191)	0.2758	.	
Chronic renal failure	Y vs N	1.223 (0.717, 2.086)	0.4735	.	
Current smoker	Y vs N	1.159 (0.768, 1.749)	0.5003	.	
Pre-hospital ACE/ARB	Y vs N	1.417 (0.997, 2.015)	0.0650	.	
Pre-hospital betablocker	Y vs N	1.355 (0.925, 1.985)	0.1308	.	
Pre-hospital statin	Y vs N	0.75 (0.493, 1.142)	0.2021	.	
Killip class	2 vs 1	1.269 (0.816, 1.975)	0.5805	.	
	3 or 4 vs 1	1.041 (0.493, 2.198)	.	.	
Serum creatinine		1 (0.998, 1.003)	0.7412	.	
Initial haemoglobin (g/L)		0.997 (0.987, 1.007)	0.4983	.	
Cardiac vessel with >=50% stenosis during cath: Left main	Y vs N	1.462 (0.957, 2.234)	0.1301	.	
Cardiac vessel with >=50% stenosis during cath: LAD	Y vs N	0.803 (0.599, 1.076)	0.1449	.	
Cardiac vessel with >=50% stenosis during cath: RCA	Y vs N	0.933 (0.702, 1.239)	0.6390	.	
Cardiac vessel with >=50% stenosis during cath: LCX	Y vs N	0.977 (0.728, 1.312)	0.8777	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

Supplementary Table 4: Patients who underwent coronary angiogram: Independent predictors of new-onset AF on admission (Basic clinical characteristics + Disease burden)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.055 (1.04, 1.069)	0.0001	1597.9487	0.797 (0.764, 0.829)
Sex	M vs F	1.498 (0.996, 2.252)	0.0571	.	
Heart rate (per min)		1.038 (1.031, 1.045)	<.0001	.	
Cardiac arrest on admission	Y vs N	2.577 (1.385, 4.796)	0.0354	.	
Hypertension	Y vs N	0.625 (0.477, 0.818)	0.0019	.	
Diabetes	Y vs N	1.001 (0.696, 1.439)	0.9959	.	
Peripheral arterial disease	Y vs N	0.866 (0.403, 1.861)	0.7060	.	

Previous stroke/transient ischemic attack	Y vs N	1.326 (0.822, 2.141)	0.2977	.	
Chronic renal failure	Y vs N	1.221 (0.73, 2.04)	0.4636	.	
Current smoker	Y vs N	1.165 (0.781, 1.738)	0.4768	.	
Pre-hospital ACE/ARB	Y vs N	1.424 (1.007, 2.015)	0.0586	.	
Pre-hospital betablocker	Y vs N	1.381 (0.949, 2.011)	0.1052	.	
Pre-hospital statin	Y vs N	0.758 (0.497, 1.154)	0.2171	.	
Killip class	2 vs 1	1.281 (0.822, 1.996)	0.5694	.	
	3 or 4 vs 1	1.018 (0.481, 2.155)	.	.	
Serum creatinine		1 (0.998, 1.003)	0.7157	.	
Initial haemoglobin (g/L)		0.997 (0.986, 1.007)	0.4646	.	
Disease burden	Single vs minor	0.783 (0.517, 1.186)	0.4774	.	
	Double vs minor	0.806 (0.62, 1.049)	.	.	
	Triple vs minor	0.741 (0.469, 1.17)	.	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

Supplementary Table 5: Patients who underwent coronary angiogram: Independent predictors of new-onset in-hospital AF (Basic clinical characteristics + Disease location)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.043 (1.034, 1.051)	<.0001	3139.0571	0.742 (0.719, 0.766)
Sex	M vs F	1.11 (0.835, 1.475)	0.4583	.	
Heart rate (per min)		1.008 (1.003, 1.013)	0.0230	.	
Cardiac arrest on admission	Y vs N	1.744 (1.129, 2.696)	0.0627	.	
Hypertension	Y vs N	1.015 (0.793, 1.299)	0.9075	.	
Diabetes	Y vs N	1.063 (0.853, 1.324)	0.5884	.	
Peripheral arterial disease	Y vs N	1.205 (0.879, 1.652)	0.2725	.	
Previous stroke/transient ischemic attack	Y vs N	1.147 (0.831, 1.584)	0.4294	.	
Chronic renal failure	Y vs N	0.98 (0.646, 1.489)	0.9256	.	
Current smoker	Y vs N	1.039 (0.818, 1.318)	0.7566	.	
Pre-hospital ACE/ARB	Y vs N	0.926 (0.738, 1.161)	0.5113	.	

Pre-hospital betablocker	Y vs N	1.427 (1.102, 1.847)	0.0262	.	
Pre-hospital statin	Y vs N	0.764 (0.601, 0.971)	0.0267	.	
Killip class	2 vs 1	1.661 (1.257, 2.193)	0.0010	.	
	3 or 4 vs 1	2.466 (1.613, 3.769)	.	.	
Serum creatinine		1 (0.999, 1.002)	0.4573	.	
Initial haemoglobin (g/L)		0.998 (0.993, 1.003)	0.4136	.	
Cardiac vessel with >=50% stenosis during cath: Left main	Y vs N	1.881 (1.368, 2.585)	0.0048	.	
Cardiac vessel with >=50% stenosis during cath: LAD	Y vs N	1.559 (1.218, 1.995)	0.0032	.	
Cardiac vessel with >=50% stenosis during cath: RCA	Y vs N	1.41 (1.156, 1.72)	0.0026	.	
Cardiac vessel with >=50% stenosis during cath: LCX	Y vs N	1.344 (1.089, 1.659)	0.0120	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

Supplementary Table 6: Patients who underwent coronary angiogram: Independent predictors of new-onset in-hospital AF (Basic clinical characteristics + Disease burden)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.043 (1.035, 1.052)	<.0001	3138.1817	0.738 (0.715, 0.762)
Sex	M vs F	1.114 (0.836, 1.483)	0.4432	.	
Heart rate (per min)		1.008 (1.003, 1.014)	0.0202	.	
Cardiac arrest on admission	Y vs N	1.753 (1.127, 2.726)	0.0632	.	
Hypertension	Y vs N	1.002 (0.785, 1.278)	0.9893	.	
Diabetes	Y vs N	1.065 (0.862, 1.316)	0.5610	.	
Peripheral arterial disease	Y vs N	1.224 (0.893, 1.678)	0.2363	.	
Previous stroke/transient ischemic attack	Y vs N	1.149 (0.836, 1.579)	0.4189	.	
Chronic renal failure	Y vs N	0.963 (0.639, 1.452)	0.8565	.	
Current smoker	Y vs N	1.03 (0.806, 1.316)	0.8119	.	
Pre-hospital ACE/ARB	Y vs N	0.925 (0.742, 1.155)	0.4992	.	
Pre-hospital betablocker	Y vs N	1.441 (1.119, 1.858)	0.0208	.	
Pre-hospital statin	Y vs N	0.764 (0.6, 0.973)	0.0272	.	
Killip class	2 vs 1	1.636 (1.24, 2.158)	0.0011	.	

	3 or 4 vs 1	2.447 (1.605, 3.732)	.	.	
Serum creatinine		1.001 (0.999, 1.002)	0.4137	.	
Initial haemoglobin (g/L)		0.998 (0.993, 1.004)	0.3589	.	
Disease burden	Single vs minor	1.283 (0.894, 1.841)	<.0001	.	
	Double vs minor	2.243 (1.577, 3.191)	.	.	
	Triple vs minor	3.346 (2.394, 4.676)	.	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

Supplementary Table 7: Casual mediation analysis (CABG as a mediator between disease location and new-onset AF)

	Left main	**LAD**	**RCA**	**LCx**
Total Effect	0.040	0.022	0.013	0.013
	[0.018, 0.061]	[0.012, 0.032]	[0.004, 0.024]	[0.004, 0.025]
	p ≤ 0.001	p ≤ 0.001	p = 0.004	p = 0.006
ACME	0.039	0.021	0.011	0.015
	[0.028, 0.048]	[0.017, 0.025]	[0.010, 0.017]	[0.012, 0.021]
	p ≤ 0.001	p ≤ 0.001	p ≤ 0.001	p ≤ 0.001
ADE	0.002	0.001	0.002	-0.002
	[-0.015, 0.018]	[-0.009, 0.012]	[-0.009, 0.012]	[-0.012, 0.009]
	p = 0.906	p = 0.818	p = 0.688	p = 0.736
Prop. Mediated	0.961	0.944	0.868	1.128
	[0.681, 1.800]	[0.605, 1.716]	[0.509, 2.687]	[0.622, 3.730]
	p ≤ 0.001	p ≤ 0.001	p = 0.004	p = 0.006

ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; Prop mediated, Proportion Mediated; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex.

Supplementary Table 8: Casual mediation analysis (CABG as a mediator between disease burden and new-onset AF)

	Single vessel	**Double vessel**	**Triple vessel**
Total Effect	0.009	0.036	0.059
	[-0.002, 0.019]	[0.019, 0.048]	[0.042, 0.079]
	p = 0.136	p ≤ 0.001	p ≤ 0.001
ACME	0.002	0.018	0.053
	[0.000, 0.005]	[0.010, 0.022]	[0.040, 0.071]

	p = 0.050	p ≤ 0.001	p ≤ 0.001
ADE	0.007	0.018	0.006
	[-0.005, 0.017]	[0.001, 0.032]	[-0.016, 0.029]
	p = 0.246	p = 0.028	p = 0.598
Prop. Mediated	0.25	0.493	0.898
	[-1.507, 2.291]	[0.272, 0.926]	[0.601, 1.350]
	p = 0.178	p ≤ 0.001	p ≤ 0.001

ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; Prop mediated, Proportion Mediated.

Sensitivity analyses: Coronary angiogram patients who did not undergo CABG

Supplementary Table 9: Coronary angiogram patients without CABG: Independent predictors of new-onset AF (Basic clinical characteristics + Disease location)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.059 (1.048, 1.069)	<.0001	2848.8086	0.764 (0.74, 0.788)
Sex	M vs F	1.068 (0.826, 1.382)	0.6090	.	
Heart rate (per min)		1.025 (1.019, 1.031)	<.0001	.	
Cardiac arrest on admission	Y vs N	2.628 (1.645, 4.198)	0.0043	.	
Hypertension	Y vs N	0.701 (0.583, 0.843)	0.0021	.	
Diabetes	Y vs N	1.046 (0.821, 1.332)	0.7195	.	
Peripheral arterial disease	Y vs N	0.828 (0.478, 1.434)	0.4970	.	
Previous stroke/transient ischemic attack	Y vs N	1.074 (0.717, 1.609)	0.7338	.	
Chronic renal failure	Y vs N	1.218 (0.83, 1.787)	0.3551	.	
Current smoker	Y vs N	1.143 (0.863, 1.513)	0.3737	.	
Pre-hospital ACE/ARB	Y vs N	1.058 (0.822, 1.363)	0.6581	.	
Pre-hospital betablocker	Y vs N	1.624 (1.131, 2.332)	0.0173	.	
Pre-hospital statin	Y vs N	0.697 (0.512, 0.947)	0.0242	.	
Killip class	2 vs 1	1.466 (1.104, 1.948)	0.0066	.	
	3 or 4 vs 1	2.262 (1.418, 3.607)	.	.	
Serum creatinine		1.001 (1, 1.003)	0.2106	.	
Initial haemoglobin (g/L)		0.996 (0.988, 1.005)	0.2690	.	
Cardiac vessel with >=50% stenosis during cath: Left main	Y vs N	0.972 (0.621, 1.521)	0.9009	.	
Cardiac vessel with >=50% stenosis during cath: LAD	Y vs N	0.949 (0.8, 1.126)	0.5437	.	

Cardiac vessel with >=50% stenosis during cath: RCA	Y vs N	1.097 (0.87, 1.384)	0.4267	.	
Cardiac vessel with >=50% stenosis during cath: LCX	Y vs N	1.066 (0.91, 1.249)	0.4373	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

Supplementary Table 10: Coronary angiogram patients without CABG: Independent predictors of new-onset AF (Basic clinical characteristics + Disease burden)

Variable	Levels	aOR (95% CI)	P-value	QIC	C-stat (95% CI)
Age		1.059 (1.049, 1.07)	<.0001	2845.0239	0.764 (0.74, 0.788)
Sex	M vs F	1.066 (0.823, 1.382)	0.6202	.	
Heart rate (per min)		1.025 (1.019, 1.03)	<.0001	.	
Cardiac arrest on admission	Y vs N	2.63 (1.646, 4.201)	0.0042	.	
Hypertension	Y vs N	0.701 (0.583, 0.843)	0.0023	.	
Diabetes	Y vs N	1.051 (0.825, 1.339)	0.6903	.	
Peripheral arterial disease	Y vs N	0.843 (0.484, 1.469)	0.5435	.	
Previous stroke/transient ischemic attack	Y vs N	1.064 (0.713, 1.588)	0.7629	.	
Chronic renal failure	Y vs N	1.223 (0.835, 1.79)	0.3460	.	
Current smoker	Y vs N	1.156 (0.874, 1.53)	0.3334	.	
Pre-hospital ACE/ARB	Y vs N	1.06 (0.825, 1.362)	0.6446	.	
Pre-hospital betablocker	Y vs N	1.627 (1.13, 2.343)	0.0177	.	
Pre-hospital statin	Y vs N	0.696 (0.512, 0.947)	0.0235	.	
Killip class	2 vs 1	1.47 (1.108, 1.951)	0.0057	.	
	3 or 4 vs 1	2.275 (1.44, 3.594)	.	.	
Serum creatinine		1.001 (1, 1.002)	0.2083	.	
Initial haemoglobin (g/L)		0.996 (0.987, 1.005)	0.2532	.	
Disease burden	Single vs minor	0.982 (0.731, 1.319)	0.4736	.	
	Double vs minor	1.185 (0.909, 1.544)	.	.	
	Triple vs minor	0.992 (0.752, 1.308)	.	.	
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; aOR, adjusted odds ratio; CI, confidence interval; QIC, quasi-likelihood under the independence model criterion; C-stat: concordance statistic					

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