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FASTTRACK CLINICAL RESEARCH
Ischaemic heart disease

New-onset atrial fibrillation and chronic coronary syndrome in the CLARIFY registry

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Abstract

Background and aims Data on new-onset atrial fibrillation (NOAF) in patients with chronic coronary syndromes (CCS) are scarce. This study aims to describe the incidence, predictors, and impact on cardiovascular (CV) outcomes of NOAF in CCS patients.

Methods Data from the international (45 countries) CLARIFY registry (prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease) were used. Among 29 001 CCS outpatients without previously reported AF at baseline, patients with at least one episode of AF/flutter diagnosed during 5-year follow-up were compared with patients in sinus rhythm throughout the study.

Results The incidence rate of NOAF was 1.12 [95% confidence interval (CI) 1.06–1.18] per 100 patient-years (cumulative incidence at 5 years: 5.0%). Independent predictors of NOAF were increasing age, increasing body mass index, low estimated glomerular filtration rate, Caucasian ethnicity, alcohol intake, and low left ventricular ejection fraction, while high triglycerides were associated with lower incidence. New-onset atrial fibrillation was associated with a substantial increase in the risk of adverse outcomes, with adjusted hazard ratios of 2.01 (95% CI 1.61–2.52) for the composite of CV death, non-fatal myocardial infarction, or non-fatal stroke, 2.61 (95% CI 2.04–3.34) for CV death, 1.64 (95% CI 1.07–2.50) for non-fatal myocardial infarction, 2.27 (95% CI 1.85–2.78) for all-cause death, 8.44 (95% CI 7.05–10.10) for hospitalization for heart failure, and 4.46 (95% CI 2.85–6.99) for major bleeding.

Conclusions Among CCS patients, NOAF is common and is strongly associated with worse outcomes. Whether more intensive preventive measures and more systematic screening for AF would improve prognosis in this population deserves further investigation.

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Structured Graphical Abstract

Key Question

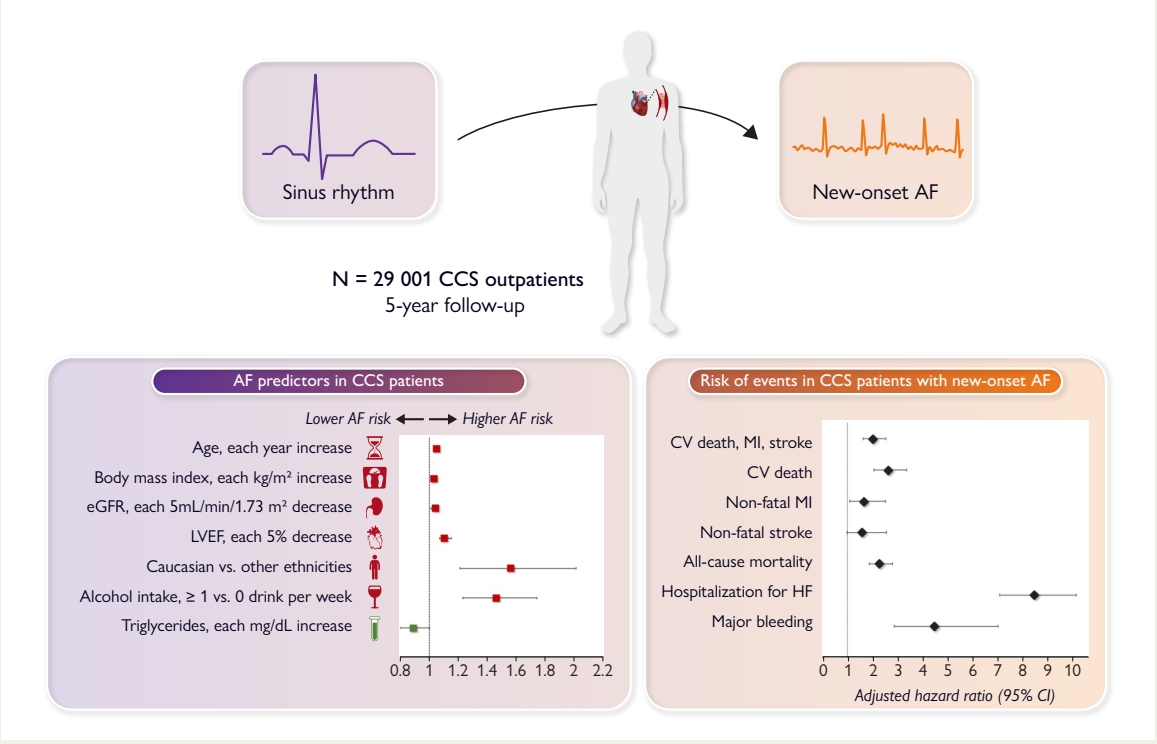
What are the incidence, predictors, and impact on cardiovascular outcomes of new-onset atrial fibrillation (NOAF) in patients with chronic coronary syndromes (CCS)?

Key Finding

- The incidence rate of NOAF in CCS outpatients detected in usual care clinical follow-up was 1.12 per 100 patient-years.
- Independent predictors were age, body mass index, Caucasian ethnicity, estimated glomerular filtration rate, alcohol consumption, left ventricular ejection fraction, and triglyceride levels.
- NOAF was associated with a substantial increase in the risk of death, non-fatal myocardial infarction, hospitalization for heart failure, and major bleeding.

Take Home Message

- NOAF is common in patients with CCS.
- Several independent predictors of NOAF in patients with CCS are identified.
- NOAF is associated with worse clinical outcomes, especially hospitalization for heart failure.



Predictors and outcomes associated with new-onset atrial fibrillation in patients with chronic coronary syndrome. AF, atrial fibrillation; CCS, chronic coronary syndrome; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Keywords Coronary artery disease • Chronic coronary syndrome • Atrial fibrillation • Risk assessment

Introduction

In recent decades, the management and prognosis of patients with chronic coronary syndromes (CCS) have improved considerably, leading to a steady decline in cardiovascular (CV) mortality.[1,2] However, some patients remain at high risk of major adverse CV events. Identifying these high-risk subsets is essential to continued progress. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated prevalence of 2%–4% in the adult population and with an incidence expected to increase continuously in the coming years.[3–5] In the general population, AF is associated with an increased risk of CV events such as stroke and heart failure (HF) as well as an increased risk of bleeding due to the frequent need for anticoagulation.[6,7] Coronary artery disease (CAD) patients share several common risk factors with AF patients such as hypertension, diabetes, and obesity,[8] and this population has a higher risk of developing AF. New-onset atrial fibrillation (NOAF) in CAD patients has mainly been studied in the setting of acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) and was consistently found to be an independent predictor of morbidity and

mortality.[9–13] In contrast, data on NOAF in patients with CCS are scarce, and better knowledge would be useful to guide their management.

This study aimed to describe the incidence and predictors of NOAF in CCS outpatients as well as its impact on major clinical outcomes using data from the international CLARIFY registry (prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease).

Methods

Population and study design

Between November 2009 and June 2010, 32 703 outpatients with CCS were enrolled in the CLARIFY registry in 45 countries, representing a wide range of geographic areas and socio-economic conditions (the list of countries is available in supplementary data). The rationale and design of the registry have been described previously.[14] Briefly, CLARIFY aimed to provide contemporary data on the clinical profile and prognosis of CCS outpatients. All patients with CAD were eligible for enrolment if they fulfilled at least one of the following non-mutually exclusive criteria: documented myocardial infarction (MI) more than 3 months before enrolment, chest pain with proven myocardial ischaemia, coronary angiography showing at least one coronary stenosis of more than 50%, CABG or PCI more than 3 months prior to enrolment. Exclusion criteria were hospitalization for CV reasons within the previous 3 months, planned revascularization, and conditions hampering participation for a 5-year follow-up [e.g. limited cooperation, limited legal capacity, serious non-CV disease, or conditions interfering with life expectancy (e.g. cancer or substance abuse), or other severe CV disease (e.g. advanced HF, severe valve disease, and history of valve repair/replacement)]. Patient enrolment was restricted to a brief period to achieve near consecutive enrolment. The study was conducted in accordance with the Declaration of Helsinki. The locally appointed ethics committee approved the research protocol, and all patients gave written informed consent.

For the present analysis, patients with a medical history of AF or flutter prior to enrolment, and those with unknown cardiac rhythm status at inclusion were excluded. New-onset atrial fibrillation was defined as the occurrence of previously unknown AF or flutter on an electrocardiogram (ECG) either at the annual visit or at another unscheduled follow-up. A trained physician collected rhythmic status at each study visit, and the date of NOAF diagnosis was specified for each patient. Chronic coronary syndrome patients who had AF or flutter episode diagnosed at least at one of the follow-up visits (NOAF patients) were compared with those who remained in sinus rhythm throughout the 5 years of follow-up (control patients).

Data collection

Data were collected using standardized electronic case report forms at baseline and annually for up to 5 years. This included demographic data, risk factors and lifestyle, medical history, physical examination, heart rhythm on a 12-lead ECG, recent biological tests results, left ventricular ejection fraction (LVEF) if available, and current medication (including β-blockers, antithrombotic, and lipid-lowering agents). To ensure the completeness and accuracy of the data, randomly selected sites underwent comprehensive data audits, in addition to regular telephone contact with investigators and centralized verification of the electronic case report forms. All patients had a minimum of one routine ECG at each annual follow-up visit.

Outcomes

For the purpose of this analysis, we pre-defined the main outcome as the composite of CV death, non-fatal MI, or non-fatal stroke. Additional outcomes of interest were each component of the composite outcome as well as all-cause mortality, hospitalization for HF, and major bleeding (defined as bleeding leading to hospitalization or blood transfusion). Events were accepted as reported by participating physicians and were not adjudicated. All events were source verified in 100% of patients in 5% of randomly selected sites which underwent audit.

Statistical analysis

Baseline characteristics were analysed according to the presence or absence of NOAF at follow-up. Categorical variables are reported as counts (and percentages) and continuous variables as mean (±standard deviation). Comparisons between groups were performed using the χ^2 test for categorical variables and Student's *t*-test for continuous variables. To determine the main predictors of NOAF, a set of univariate Cox proportional hazards models was first conducted for assessing the individual impact of a pre-defined list of potential predictors. Each predictor showing an effect with a *P*-value $\leq .2$ in the univariate model was then selected and introduced in a multivariate Cox model. Hazard ratios (HR), 95% confidence intervals (CI), and related *P*-values estimated in these models were reported. The potential predictors investigated in this analysis were: age, gender, Caucasian ethnicity, body mass index (BMI), treated hypertension, diabetes, smoking status, consumption of alcohol, tea or coffee, the level of physical activity, medical history of MI, PCI, CABG, peripheral artery disease, stroke, asthma/chronic obstructive pulmonary disease (COPD), blood levels of triglycerides (TG), low-density lipoprotein cholesterol (LDLc), haemoglobin, and estimated glomerular filtration rate (eGFR), LVEF, current medication with β-blockers, or non-dihydropyridine calcium channel blockers. Five-year event rates with their 95% CIs were estimated by Kaplan–Meier (KM) method. For the NOAF-induced risk analysis, the adjustment variables were: age, sex, geographic origin, diabetes, hypertension, current smoking, history of peripheral artery disease, prior MI, prior stroke, and chronic HF. Patients lost to follow-up were censored at the time of their last information collected. For risk analyses assessing the impact of NOAF on study outcomes, the occurrence of AF variable was introduced as a time-varying covariate in the Cox model. A two-tailed $P \leq .05$ was considered statistically significant. Analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline demographic data

Among 32 703 outpatients with CCS, 2312 (7.1%) had a medical history of AF or flutter and 1390 (4.2%) had missing data regarding their rhythm status at baseline and were excluded. Therefore, the present analysis focused on 29 001 CCS patients without AF or flutter at baseline. The study flowchart is represented in *Figure 1*. At the end of the 5-year follow-up, 1453 patients (5.0%) had NOAF diagnosed, and they were compared to patients without AF. Baseline characteristics according to AF status are displayed in *Table 1* and show substantial differences between the two groups. Compared to patients who remained in sinus rhythm, patients with NOAF were older (68.3 ± 9.6 vs. 63.4 ± 10.4 years, $P < .001$), more often Caucasian (76.3% vs. 63.3%, $P < .001$), had more risk factors: smoking (60.9% vs. 58.8%, $P = .008$), diabetes (32.3% vs. 28.9%, $P = .017$), treated hypertension (77.5% vs. 70%, $P < .001$), dyslipidaemia (80.1% vs. 74.6%, $P < .001$), and higher BMI (28.7 ± 4.9 vs. 27.8 ± 4.5, $P < .001$), had more extensive atherosclerotic disease: CABG (29.1% vs. 22.4%, $P < .001$), peripheral artery disease (14.2% vs. 9.2%, $P < .001$), aortic abdominal aneurysm (2.1% vs. 1.3%, $P = .03$), and carotid disease (10% vs. 7.1%, $P < .001$), lower LVEF (54.0 ± 11.6% vs. 56.4 ± 10.8%, $P < .001$), more prior permanent pacemaker or implantable cardioverter defibrillator (5.6% vs. 2.4%, $P < .001$), more history of hospitalization for HF (7.4% vs. 3.6%, $P < .001$), asthma/COPD (10.4% vs. 6.7%, $P < .001$), and weekly alcohol intake (59.5% vs. 51.5%, $P < .001$). CHA_2DS_2-VASc score was also

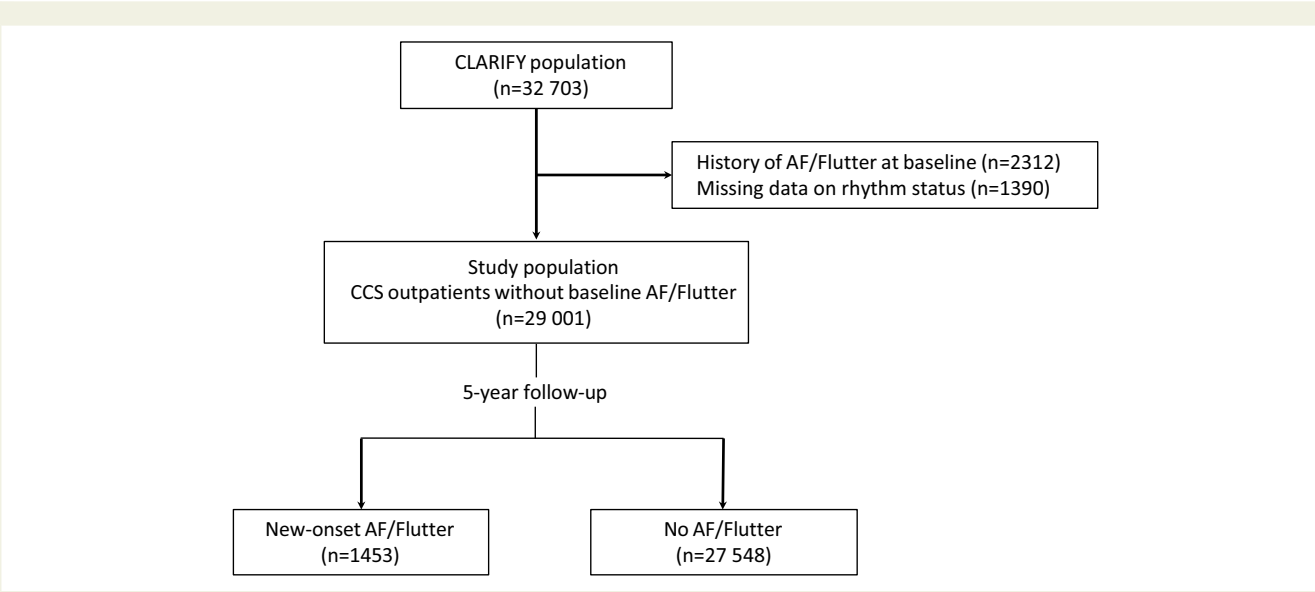


Figure 1 Flowchart. AF, atrial fibrillation; CCS, chronic coronary syndrome; CLARIFY, prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease.

higher (3.5 ± 1.3 vs. 3.0 ± 1.3, $P < .001$). Regarding biological parameters, patients with NOAF had lower haemoglobin (13.9 ± 1.5 vs. 14.0 ± 1.5 g/dL, $P = .01$), higher high-density lipoprotein cholesterol (HDLc) (47.5 ± 12.6 vs. 45.9 ± 12.6 mg/dL, $P < .001$), lower TG (1.5 ± 0.8 vs. 1.6 ± 0.8 mg/dL, $P = .007$), and similar LDLc levels compared with patients in sinus rhythm. No differences were observed between groups regarding the use of guideline-recommended secondary prevention pharmacological therapies. Patients with NOAF had a longer prior history of CAD than patients in sinus rhythm (8.5 ± 7.2 vs. 6.2 ± 6 years, $P < .001$). In this population, the mean lag between the diagnosis of CAD and the onset of AF was 11.2 ± 7.3 years.

Incidence and predictors of new-onset atrial fibrillation in chronic coronary syndrome patients

The cumulative incidence of NOAF at 5 years was 5.0% with an incidence rate of 1.12 (1.06–1.18) per 100 patient-years. Independent predictors of NOAF are shown in *Table 2* and included increasing age [HR 1.05 (95% CI 1.04–1.06) per 1-year increase], Caucasian ethnicity [HR 1.56 (95% CI 1.21–2.01)], higher BMI [HR 1.03 (95% CI 1.01–1.05) for each 1 kg/m^2 increase], low LVEF [HR 1.10 (95% CI 1.07–1.15) for each 5% decrease], low eGFR [HR 1.04 (95% CI 1.01–1.06) for each 5 mL/min/1.73 m^2 decrease], and alcohol intake ≥1 drink per week [HR 1.46 (95% CI 1.23–1.74)], whereas higher TG levels were associated with a lower risk of AF [HR 0.89 (95% CI 0.80–1.00) for each 1 mg/dL increase].

Clinical outcomes

Compared to patients without AF, CCS patients with NOAF experienced worse outcomes at 5-year follow-up. Event rates estimated by KM and adjusted HRs for the primary composite endpoint (CV death, non-fatal MI, or non-fatal stroke) were 16.5% vs. 7.8% (HR 2.01, 95% CI 1.61–2.52) for NOAF vs. sinus rhythm patients. Likewise, KM rates were 7.0% vs. 4.3% for CV death (HR 2.61, 95% CI 2.04–3.34), 6.7% vs. 3.4% for non-fatal MI (HR 1.64, 95% CI 1.07–2.50), 6.8% vs. 1.9% for non-fatal stroke (HR 1.57, 95% CI 0.97–2.54), 9.3% vs. 7.1% for all-cause death (HR 2.27, 95% CI 1.85–2.78), 16.1% vs. 4.0% for hospitalization for HF (HR 8.44, 95% CI 7.05–10.10), and 5.1% vs. 1.1% for major bleeding (HR 4.46, 95% CI 2.85–6.99) (*Table 3* and Supplementary data online, *Table S1*). Event rates by CHA_2DS_2-VASc score and history of myocardial infarction are reproted in Supplementary material online, *Tables S2* and *S3*. Event rates excluding patients on anticoagulant and/or amiodarone at baseline are reported in *Table S4*.

Discussion

To the best of our knowledge, this is the largest study to date assessing the impact of incident AF in CCS patients and provides several important observations. Over a 5-year follow-up, nearly 5% of CCS patients had NOAF diagnosed with an incidence rate of 1.12 per 100 patient-years, which was higher than in the general population where the observed rate is 0.32 per 100 patient-years.[15] The baseline prevalence of AF or flutter in CCS patients from CLARIFY was 7.1%, which was somewhat higher than that described in the general population in the same age range of 65–69 years, where the prevalence has been reported to be 5.5% for men and 2.7% for women.[3] The mean age at NOAF diagnosis was lower in the CCS population than in the general population (68.3 ± 9.6 vs. 78.0 ± 12.3 years).[15] These data are consistent with the higher risk of developing AF in CAD patients compared to the general population.[16] The main predictors of NOAF among CCS patients in our study were increasing age and BMI, Caucasian ethnicity, low LVEF and eGFR values, and alcohol consumption, whereas elevated TG levels were associated with a lower incidence of AF. New-onset atrial fibrillation was associated with a marked increase in the risk of adverse CV events, including major bleeding, with the increase being most prominent for the risk of hospitalization for HF (*Structured Graphical Abstract*).

There is a potential two-way interaction between the pathophysiology of AF and CAD. On one hand, AF may participate in the progression of CAD by exacerbating endothelial dysfunction and systemic inflammation.

Table 1 Baseline demographics by rhythm status

	Overall CLARIFY population $n = 29\,001$	NOAF patients $n = 1453$	Sinus rhythm patients $n = 27\,548$
Age (years)	63.7 ± 10.4	68.3 ± 9.6	63.4 ± 10.4
Male sex	22 484 (77.5%)	1138 (78.3%)	21 346 (77.5%)
Ethnicity			
Caucasian	18 560 (64.0%)	1108 (76.3%)	17 452 (63.3%)
South Asian	2257 (7.8%)	37 (2.5%)	2220 (8.0%)
Chinese	2552 (8.8%)	72 (5.0%)	2480 (9.0%)
Japanese/Korean	982 (3.4%)	13 (0.9%)	969 (3.5%)
Hispanic	1419 (4.9%)	64 (4.4%)	1355 (4.9%)
Black/African	301 (1.0%)	12 (0.8%)	289 (1.0%)
Unknown	2930 (10.1%)	147 (10.1%)	2783 (10.1%)
Risk factors and lifestyle			
Hypertension	20 404 (70.4%)	1126 (77.5%)	19 278 (70.0%)
Diabetes	8422 (29.0%)	470 (32.3%)	7952 (28.9%)
Dyslipidaemia	21 707 (74.8%)	1164 (80.1%)	20 543 (74.6%)
Smoking status			
Current	3717 (12.8%)	153 (10.5%)	3564 (12.9%)
Former	13 370 (46.1%)	732 (50.4%)	12 638 (45.9%)
Never	11 914 (41.1%)	568 (39.1%)	11 346 (41.2%)
Family history of premature CAD	8284 (28.6%)	407 (28.0%)	7877 (28.6%)
Alcohol intake			
0 drink per week	13 940 (48.1%)	588 (40.5%)	13 352 (48.5%)
≥1 drinks per week	15 056 (51.9%)	865 (59.5%)	14 191 (51.5%)
>0 and <20	14 008 (48.3%)	795 (54.7%)	13 213 (48.0%)
20–40	950 (3.3%)	64 (4.4%)	886 (3.2%)
>40	98 (0.3%)	6 (0.4%)	92 (0.3%)
Stimulant drink consumption			
Coffee	13 748 (47.4%)	696 (48.0%)	13 052 (47.4%)
Tea	8958 (30.9%)	410 (28.3%)	8548 (31.0%)
Neither	6281 (21.7%)	345 (23.8%)	5936 (21.6%)
Physical activity			
No physical activity weekly	4523 (15.6%)	276 (19.0%)	4247 (15.4%)
Only light physical activity in most weeks	14 897 (51.4%)	729 (50.2%)	14 168 (51.4%)
Vigorous physical activity ≥20 min once or twice a week	4946 (17.0%)	241 (16.6%)	4705 (17.1%)
Vigorous physical activity ≥20 min ≥3 times per week	4628 (16.0%)	207 (14.2%)	4421 (16.0%)
Past medical history			
Myocardial infarction	17 509 (60.4%)	873 (60.1%)	16 636 (60.4%)
PCI	17 211 (59.3%)	754 (51.9%)	16 457 (59.7%)
CABG	6596 (22.7%)	423 (29.1%)	6173 (22.4%)
Peripheral artery disease	2730 (9.4%)	206 (14.2%)	2524 (9.2%)

Continued

Table 1 *Continued*

	Overall CLARIFY population *n* = 29 001	NOAF patients *n* = 1453	Sinus rhythm patients *n* = 27 548
Aortic abdominal aneurysm	392 (1.3%)	31 (2.1%)	361 (1.3%)
Carotid disease	2100 (7.2%)	146 (10.0%)	1954 (7.1%)
Stroke	1695 (5.8%)	131 (9.0%)	1564 (5.7%)
LVEF (%)	56.3 ± 10.9	54.0 ± 11.6	56.4 ± 10.8
Previous PM or ICD	732 (2.5%)	82 (5.6%)	650 (2.4%)
Hospitalization for heart failure	1094 (3.7%)	107 (7.4%)	987 (3.6%)
CHA_2DS_2-VASc score	3.1 ± 1.3	3.5 ± 1.3	3.0 ± 1.3
Asthma/COPD	2007 (6.9%)	151 (10.4%)	1856 (6.7%)
BMI (kg/m^2)	27.8 ± 4.6	28.7 ± 4.9	27.8 ± 4.5
Laboratory results			
HbA1c (%)	6.8 ± 1.7	6.7 ± 1.1	6.8 ± 1.8
Total cholesterol (mg/dL)	171.6 ± 41.7	172.1 ± 41.7	171.6 ± 41.7
LDL-cholesterol (mg/dL)	96.9 ± 34.1	96.8 ± 32.9	96.9 ± 34.2
HDL-cholesterol (mg/dL)	46 ± 12.6	47.5 ± 12.6	45.9 ± 12.6
Triglycerides (mg/dL)	1.6 ± 0.9	1.5 ± 0.8	1.6 ± 0.8
Haemoglobin (g/dL)	14.0 ± 1.5	13.9 ± 1.5	14.0 ± 1.5
Creatinine (μmol/L)	21.6 ± 342.8	27.0 ± 435.3	21.3 ± 336.9
Baseline medications			
Antiplatelet therapy	28 090 (96.9%)	1392 (95.8%)	26 698 (96.9%)
Single antiplatelet therapy	19 745 (68.1%)	1051 (72.3%)	18 694 (67.9%)
Dual antiplatelet therapy	8345 (28.7%)	341 (23.5%)	8004 (29.0%)
Oral anticoagulants	1482 (5.1%)	113 (7.8%)	1369 (5.0%)
Lipid-lowering agents (any)	26 873 (92.7%)	1345 (92.6%)	25 528 (92.7%)
Statins	24 154 (83.3%)	1206 (83.0%)	22 948 (83.3%)
Beta-blockers	21 864 (75.4%	1092 (75.1%)	20 772 (75.4%)
Amiodarone	503 (1.7%)	58 (4.0%)	445 (1.6%)
Ivabradine	2988 (10.3%)	189 (13.0%)	2799 (10.2%)
Calcium channel blockers	7888 (27.2%)	474 (32.6%)	7414 (26.9%)
ACE-inhibitors	14 969 (51.6%)	800 (55.1%)	14 169 (51.4%)
ARBs	7623 (26.3%)	433 (29.8%)	7190 (26.1%)

New-onset atrial fibrillation patients were defined as all patients without AF at entry into the CLARIFY study who subsequently developed AF at any time during the 5-year follow-up. Patients in sinus rhythm were defined as all patients without diagnosed AF throughout the 5-year follow-up. Data are presented as number (%) for categorical variables or mean ± standard deviation for continuous variables. Categorical and continuous variables were compared across groups by χ^2 test and Student's *t*-test, respectively.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; PM, pacemaker; SD, standard deviation.

On the other hand, the presence of CAD, potentially causing atrial ischaemia or infarction, can promote AF through various mechanisms (re-entry phenomena, focal ectopic activity, autonomic imbalance in favour of the sympathetic system) which, associated with oxidative stress, especially during ACS, can trigger the onset of AF.[17]

Although several data exist on AF in various CAD populations, particularly after ACS or CABG, very little is known in the CCS population. The incidence and impact of NOAF in patients with ACS was assessed in the large Danish national registry, in comparison to patient without AF prior to or during ACS.[18] New-onset atrial fibrillation had an incidence rate of 4.0% at admission and was strongly associated with an increased risk of stroke (HR 1.67; 95% CI 1.38–2.01), all-cause death (HR 1.52; 95% CI 1.43–1.62) and bleeding (HR 1.28; 95% CI 1.15–1.43) at 1 year of follow-up. In the CCS population of the CLARIFY registry,

Table 2 Predictors of new-onset atrial fibrillation in chronic coronary syndrome patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, for each 1-year increase	1.05 (1.05–1.06)	<.001	1.05 (1.04–1.06)	<.001
Male (yes vs. no)	1.06 (0.93–1.20)	.399		
Caucasian (yes vs. no)	1.66 (1.47–1.87)	<.001	1.56 (1.21–2.01)	<.001
Hypertension (yes vs. no)	1.45 (1.29–1.65)	<.001	1.18 (0.96–1.46)	.114
Diabetes (yes vs. no)	1.21 (1.08–1.35)	<.001	1.02 (0.85–1.21)	.856
Peripheral artery disease (yes vs. no)	1.73 (1.50–2.01)	<.001	1.24 (0.98–1.56)	.075
Smoking status (former/current vs. no)	1.09 (0.98–1.21)	.125		
Alcohol intake, ≥1 vs. 0 drink per week	1.36 (1.22–1.51)	<.001	1.46 (1.23–1.74)	<.001
Coffee (≥1cup/day vs. none)	0.63 (0.09–4.45)	.643		
Tea (≥1cup/day vs. none)	0.10 (0.01–0.74)	.024		
Physical activity (yes vs. no)	0.75 (0.66–0.86)	<.001	1.09 (0.87–1.37)	.441
Myocardial infarction (yes vs. no)	0.99 (0.89–1.10)	.865		
PCI (yes vs. no)	0.73 (0.66–0.81)	<.001	0.95 (0.80–1.13)	.547
CABG (yes vs. no)	1.41 (1.26–1.58)	<.001	0.92 (0.76–1.12)	.422
Stroke (yes vs. no)	1.67 (1.40–2.00)	<.001	1.31 (1.00–1.72)	.053
Asthma/COPD	1.64 (1.38–1.94)	<.001	1.02 (0.77–1.34)	.903
BMI, for each 1 kg/m^2 increase	1.04 (1.03–1.05)	<.001	1.03 (1.01–1.05)	<.001
LDL-cholesterol, for each 1 mg/dL increase	1.00 (1.00–1.00)	.976		
Triglycerides, for each 1 mg/dL increase	0.88 (0.82–0.95)	<.001	0.89 (0.80–1.00)	.041
Haemoglobin, for each 1 g/dL increase	0.94 (0.90–0.97)	<.001	0.98 (0.92–1.03)	.420
eGFR, for each 5 mL/min/1.73 m^2 decrease	1.09 (1.07–1.10)	<.001	1.04 (1.01–1.06)	.004
LVEF for each 5% decrease	1.10 (1.07; 1.13)	<.001	1.10 (1.07–1.15)	<.001
Beta-blockers (yes vs. no)	0.97 (0.86–1.09)	.623		
Calcium-channel blockers (verapamil or diltiazem) (yes vs. no)	1.32 (1.18–1.47)	<.001	1.09 (0.91–1.30)	.340

The multivariate model used variables with a *P*-value <.2 in the univariate model.
AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation; HR, hazard ratio; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.

we observed that this NOAF-induced risk was even higher. However, a direct comparison using adequate comparable groups is not available and therefore cannot be ascertained. It has been reported that NOAF following an ACS worsens in-hospital prognosis but does not appear to affect long-term prognosis in those who survive to hospital discharge.[19]

Otterstad *et al.*[20] previously assessed the impact of NOAF in a smaller population of selected patients with stable symptomatic CAD ($n = 7665$) in a *post hoc* analysis of the randomized ACTION trial (A Coronary disease Trial Investigating Outcome with Nifedipine). Over a 5-year follow-up, 7.8% patients had developed NOAF with incidence rate of 1.64 per 100 patient-years, slightly higher than our observations in CLARIFY. This can be explained in two ways: first, follow-up was more frequent in the ACTION trial (every 6 months vs. annually), second, the population enrolled was at higher risk than in the CLARIFY registry as the former only enrolled patients with angina, and LVEF was lower (47.6% vs. 54%). The occurrence of AF in this CAD population was associated with an impaired prognosis compared to patient without AF. Our study reached a similar conclusion, showing very clearly that NOAF dramatically increased the risk of major adverse outcomes in the CCS population, including death, MI, stroke, HF, but also of bleeding risk. Indeed, the diagnosis of AF requires an upward revision of the antithrombotic regimen to prevent the induced risk of a cardio-embolic event. The association of AF and CCS therefore places a heavy burden on patients' prognosis and on healthcare systems. As the CLARIFY registry only included patients with CCS, the magnitude of this NOAF-induced risk compared to the general population is unclear. Nevertheless, compared to other studies which evaluated the impact of NOAF in the general population, the risk of HF and ischaemic stroke seemed to be in the same proportion as in our study, with the difference that median age of occurrence was lower in our CCS cohort.[21]

Table 3 Five-year risk of events induced by new-onset atrial fibrillation in patients with chronic coronary syndrome

	Adjusted HR (95% CI) time-varying analysis ($n = 29\,001$)	*P*-value
CV death, non-fatal MI, and non-fatal stroke	2.01 (1.61–2.52)	<.001
CV death	2.61 (2.04–3.34)	<.001
Non-fatal MI	1.64 (1.07–2.50)	.023
Non-fatal stroke	1.57 (0.97–2.54)	.066
All-cause death	2.27 (1.85–2.78)	<.001
Hospitalization for heart failure	8.44 (7.05–10.10)	<.001
Major bleeding	4.46 (2.85–6.99)	<.001

Hazard ratios were adjusted and estimated from a multivariable Cox proportional hazards model. New-onset of AF has been introduced as time-varying covariate. Adjustment variables: Age, sex, geographic origin, diabetes, hypertension, smoking (current), peripheral artery disease, prior MI, prior stroke, and chronic heart failure.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

The predictive factors of NOAF identified in our study are consistent with those in the general population.[22,23] We also found an increased risk of AF for the Caucasian population, which is consistent with the findings of Dewland *et al.*[24] Among the modifiable factors, alcohol consumption was one of the most strongly associated with AF. The increased risk cut-off for incident AF was previously reported for a regular alcohol consumption of only 2 g/day, or a little <1 drink/week, similar to the threshold used in our analysis.[23] Abstinence from alcohol has been shown to effectively reduce AF burden. Therefore, given the poor prognosis induced by NOAF in patients with CCS, alcohol abstinence may be an additional preventive measure to be seriously explored in this population.[25,26]

Interestingly, elevated TG levels were associated with a lower risk of AF. A conflicting body of literature exists on the dyslipidaemia paradox associated with NOAF. The ARIC (Atherosclerosis Risk In Communities) study found that elevated levels of LDLc and total cholesterol were associated with a lower incidence of NOAF whereas HDLc and TG were not.[27] Similar results were found in large, observational Swedish and Chinese studies[28,29] whereas Watanabe *et al.*[30] found that low HDLc but not TG levels were associated with an increased risk of NOAF in women. In the recent REDUCE-IT randomized trial[31] of patients with elevated TG levels, the endpoint of hospitalization for AF or flutter was increased in the group receiving icosapent-ethyl as compared to the placebo group (3.1% vs. 2.1%, $P = .004$). Similar observations have been made across several studies of omega-3 fatty acids that aimed to lower TG levels.[32]

Our results call for further studies to evaluate whether additional preventive measures, such as alcohol abstinence, weight loss, TG monitoring, and closer follow-up of HF, could prevent the onset of AF and improve the prognosis of patients with CCS.

Ambulatory AF screening is changing with the advent of wearable devices that have potential advantages over usual screening tools.[33] However, more intensive NOAF screening compared to usual care is only cost-effective in selected at-risk patients.[34–36] Chronic coronary syndrome patients therefore represent a population in whom the use of these modern digital tools should be tested.

The LOOP randomized trial previously compared AF detection by continuous ECG monitoring using an implantable loop recorder with an ECG performed annually at a usual care follow-up visit in a high-risk population.[37] Intensive screening with the loop recorder resulted in a three-fold increase in AF detection and anticoagulation initiation. However, this did not translate into a significant reduction in the risk of stroke or peripheral embolism. Therefore, there remains uncertainty regarding the clinical implications of detecting brief asymptomatic episodes of AF, in terms of anticoagulation initiation. Patients with CCS constitute a group at high risk of major clinical events, and future studies are needed to assess whether intensive AF detection will provide clinical benefit, what the impact of AF burden is, and what the optimal antithrombotic strategy is.

Limitations and strengths

Our study has several limitations. First, the CLARIFY registry consisted of a relatively young population with preserved LVEF and wide use of evidence-based secondary prevention treatments. This reflects the exclusion of patients with severe non-cardiac disease or advanced cardiac conditions, such as advanced HF or severe heart valve disease. The diagnosis of AF was based on an ECG performed either at the annual study visit or at another unscheduled follow-up, so transient episodes may have been missed. Additionally, patients who developed NOAF and died before the next visit could be missed. For these reasons, the true incidence of AF in the global CCS population has most likely been underestimated. Given the results of the LOOP trial, NOAF incidence may be much higher than observed in our study, potentially up to three-fold higher. Among other limitations, the impact of AF burden could not be assessed since the CLARIFY registry was not designed to detect asymptomatic AF. However, the clinical benefit of intensive AF screening in a CCS population remains to be demonstrated.

Whether medical therapy associated with AF diagnosis might have influenced prognosis could not be evaluated in our cohort. Nevertheless, the AFIRE trial previously showed that direct oral anticoagulant monotherapy with rivaroxaban was non-inferior to combination therapy with rivaroxaban plus a single antiplatelet therapy regarding efficacy and superior for safety in CCS patients with AF.[38]

There was more use of anticoagulant therapy and amiodarone at baseline among NOAF patients. Although such treatments can sometimes be prescribed for other indications, this suggests that a prior diagnosis of AF may have been underreported in this group. However, the absolute number of patients receiving these agents was quite small (113 and 58 patients on anticoagulants or amiodarone, respectively in the NOAF group), and this would only have a modest impact on our estimation of AF incidence.

The strengths of our study were the large number of patients included with a wide geographical distribution and a complete follow-up for the vast majority of them.

Clinical implications and perspectives

Coronary artery disease remains the first cause of death worldwide and AF the most common sustained cardiac arrhythmia with a steadily increasing prevalence. Due to the ageing of the population and the improved long-term prognosis of CAD patients, the overlap of CCS and AF is a concern for the future. Occurrence of AF in CCS patients appeared to be strongly associated with major adverse events and represents an important prognostic factor. Whether more intensive preventive measures and screening for AF would result in improved outcomes is unknown at this stage and deserves further study.

Conclusion

The incidence rate of NOAF in CCS outpatients detected in usual care clinical follow-up was 1.12 per 100 patient-years with several predictors identified. Occurrence of AF was associated with a markedly increased risk of major adverse events and thus weighs heavily on the prognosis of CCS patients and on healthcare systems. Further study is needed to assess the impact of more intensive preventive measures and more systematic screening for AF in the CCS population.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.G. reports consulting fees from GE Healthcare and Terumo, outside the submitted work. F.P. reports consulting fees from BBraun, Biotronik, Boston Scientific, personal fees from Bayer, Biotronik, BMS-Pfizer Alliance, outside the submitted work. G.D. reports personal fees Abbott, Amgen, Astra Zeneca, Bayer, BMS, Novo Nordisk, Sanofi, Boston scientific, outside the submitted work. Y.E. has nothing to disclose. K.M.F. reports personal fees and non-financial support from Servier, during the conduct of the study, personel fees from TauRx, outside the submitted work. He is Director of Vesalius Trials Ltd. R.F. reports grants and personal fees from Servier, Merck Serono, Sunpharma, Lupin, Reddys, outside the submitted work. He is a director of Art Research and Science S.r.l (A.R.S.1) and scientific director of Medical Trial Analysis. I.F. reports grants and personal fees from Servier, during the conduct of the study, outside the submitted work. J.C.T. reports grants and personal fees from Servier, during the conduct of the study; grants from Amarin, AstraZeneca, Ceapro, Esperion, Ionis, Merck, Novartis, Pendopharm and Pfizer and RegenXBio, personal fees and minor equity interest in DalCor Pharmaceuticals, outside the submitted work. M.T. reports personal fees from Servier, during the conduct of the study; consulting fees from Bayer, Janssen-Cilag, Kowa, PERFUSE Group, personal fees from Bayer, outside the submitted work. P.G.S. reports grants and personal fees from Servier, during the conduct of the study, grants from Amarin, Bayer, Sanofi, Servier, consulting fees from Amarin, Amgen, AstraZeneca, Bayer, BMS/Myokardia, Boehringer Ingelheim, Bristol-Myers Squibb, Idorsia, Merck, Novartis, Novo-Nordisk, Pfizer, PhaseBio, Regeneron, Sanofi, Servier, personal fees from AstraZeneca, Novartis and Novo Nordisk, outside the submitted work.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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The CLARIFY registry was supported by Servier. The sponsor had no role in the study design, data analysis and interpretation, or decision to submit the manuscript for publication, but assisted with the set-up, data collection, and management of the study in each country. The corresponding author had full access to all data and had the final responsibility for the decision to submit for publication.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki. The locally appointed ethics committee approved the research protocol and all patients gave written informed consent.

Pre-registered Clinical Trial Number

The pre-registered clinical trial number is ISRCTN43070564.

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Correction

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Correction to: Fulminant myocarditis proven by early biopsy and outcomes

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In the originally published version of this manuscript, there was a typographic error in the author list.

This error has been corrected.