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Antithrombotic management of patients with acute coronary syndromes and atrial fibrillation undergoing coronary stenting: a prospective, observational, nationwide study

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ABSTRACT

Objective. The aim of the study was to assess current management of patients with atrial fibrillation (AF) and acute coronary syndromes (ACS) undergoing coronary stenting.

Design. Non-interventional, prospective, nationwide study.

Setting. 76 private or public cardiology centers in Italy.

Participants. ACS patients with concomitant AF undergoing percutaneous coronary intervention (PCI).

Primary and secondary outcome measures. To obtain accurate and up-to-date information on pharmacological management of patients with AF admitted for an ACS and undergoing PCI with stent implantation.

Results. Over a 12-month period, 598 consecutive patients were enrolled: 48.8% with AF at hospital admission and 51.2% developing AF during hospitalization. At discharge, a triple antithrombotic therapy (TAT) was prescribed in 64.8%, dual antiplatelet therapy (DAPT) in 25.7%, and dual antithrombotic therapy (DAT) in 8.8% of patients. Among patients with AF at admission, TAT and DAT were more frequently prescribed compared to new onset AF patients (76.3% vs 53,8% and 12.5% vs 5.3%, respectively; both p<0.0001), while a DAPT was less often used (11.2% vs 39.5%; p<0.0001). At multivariable analysis, a history of major bleeding [odds ratio (OR): 5.40; 95% confidence intervals (CI): 2.42-12-05; p<0.0001] and malignancy (OR: 5.11; 95% CI: 1.77-14.78; p=0.0026) resulted the most important independent predictors of DAT prescription.

Conclusions. In this contemporary registry of ACS patients with AF treated with coronary stents, TAT still resulted as the antithrombotic strategy of choice, DAT was reserved for high bleeding risk and DAPT was mainly prescribed in those developing AF during hospitalization.

Key words: acute coronary syndromes; atrial fibrillation; percutaneous coronary intervention; stents; direct oral anticoagulants; treatment.

Strengths and limitations of this study

- Prospective, nationwide observational study
- Contemporary community-based registry evaluating the antithrombotic management of patients with ACS and AF undergoing PCI
- Data limited to the hospitalization period

INTRODUCTION

Approximately 10% of patients with acute coronary syndromes (ACS) requiring percutaneous coronary intervention (PCI) with stent implantation presents a concomitant atrial fibrillation (AF) (1-11). Such patients theoretically need oral anticoagulation (OAC) and dual antiplatelet therapy (DAPT), a combination known as triple antithrombotic therapy (TAT), in order to decrease both the risk of thromboembolism due to AF and the risk of thrombosis and recurrent ischemic events due to ACS and coronary stents (1-7). Unsurprisingly, TAT is associated with a high rate of major and fatal bleeding events (12). Recently, several randomized trials demonstrated the favorable safety profile of a double antithrombotic therapy (DAT), which combines OAC with a P2Y12 receptor inhibitor, as compared to TAT (13-17).

After the validation of these novel antithrombotic strategies and the dissemination of direct oral anticoagulants (DOACs) in clinical practice, no nationwide or community-based data describing contemporary pharmacological management of patients with AF and ACS treated with PCI are available. In this regard, the Italian National Association of Hospital Cardiologist (ANMCO) designed the MATADOR-PCI (Management of Antithrombotic TherApy in Patients with Chronic or DevelOping AtRial Fibrillation During Hospitalization for PCI) study, aimed to obtain accurate and up-to-date information concerning management and outcome of patients with AF admitted in cardiology intensive care units (CCUs) for an ACS undergoing PCI with stent implantation.

METHODS

The MATADOR-PCI was a prospective, observational, nationwide registry of consecutive patients with a confirmed diagnosis of ACS treated with PCI and concomitant AF conducted in Italy during a 1-year period.

All consecutive ACS patients [non-ST elevation-ACS (NSTE-ACS) or ST-elevation myocardial infarction (STEMI)] undergoing PCI and with AF at the time of hospital admission, either paroxysmal, persistent or permanent, or developing during the index hospitalization were included. Patients admitted with a diagnosis of ACS at the time of enrolment but not confirmed during hospitalization, ACS treated medically, with surgical revascularization or with percutaneous coronary balloon angioplasty without stent implantation, and those not giving informed consent were excluded from the survey. Enrolment was made at hospital discharge.

ANMCO invited to participate in this study all Italian cardiology centers with a CCU and a catheterization laboratory performing at least 400 PCI per year (medium-high volume according to Italian standards), including university teaching hospitals, general and regional hospitals, and private clinics. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during this observational study. However, current guidelines for the management of patients with AF, myocardial revascularization and ACS have been discussed during the investigator meetings.

Data collection and data quality

Data on demographics, cardiovascular and non-cardiovascular medical history, previous interventional procedures, type of ACS, type of AF, the timing of AF onset (if AF occurred during hospitalization), in-hospital management, pharmacological treatment, timing of PCI, severity and extension of coronary artery disease, number and type of stent, laboratory values, ECG characteristics, hemodynamic parameters, and in-hospital major clinical events were collected.

Myocardial infarction was defined according to the third universal definition of MI (18). Stroke was identified as an acute neurologic deficit lasting >24 hours and affecting the ability to perform daily activities with or without confirmation by imaging techniques. Stent thrombosis was defined according to the Academic Research Consortium (ARC) recommendations (19). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria (20). A major bleeding was defined as BARC ≥3.

At each site, the principal investigator was responsible for screening eligible consecutive patients. Data were collected using a web-based, electronic CRF with the central database located at the ANMCO Research Center. By using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range.

Patient consent and ethical approval

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) approved the study protocol according to the current Italian rules.

The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines and the applicable local legislations of non-interventional studies. The MATADOR-PCI study is registered at ClinicalTrials.gov (NCT03656523).

Statistical analysis

Considering the explorative and observational nature of the study, no formal sample size calculation has been performed. However, considering the number of ACS patients with AF at the time of hospital admission or developing AF during the index hospitalization enrolled in previous snapshots performed in Italy and endorsed by ANMCO in the last 15 years (21), it was estimated to include approximately 500 patients (8% of ACS patients undergoing PCI in 1 year in about 100 centers) to allow for a representative national cohort in terms of

geographical distribution and well balanced in terms of complexity (e.g. PCI volume, cardiac surgery).

Normally distributed variables were expressed as mean ± standard deviation (SD), and compared using the Student t test, whereas non-normally distributed variables as median and interquartile range (IQR) and compared with the Mann-Whitney U test. Categorical variables were reported as numbers and percentages and compared using the chi-squared test or Fisher exact tests, as appropriate.

The study cohort was stratified according to the two pre-specified groups of patients: (1) those with AF at the time of hospital admission and (2) those developing AF after hospital admission for an ACS.

Clinically relevant variables which were significant at univariate analysis were included in a multivariable model (logistic regression) was performed using significant variables at univariate analysis in order to identify the independent predictors of DAT prescription at discharge. The variables included in the logistic model were: age (<65 reference group, 65-74, ≥75 years), gender, onset of AF (at admission vs during hospitalization), type of ACS (STEMI vs NSTE-ACS), diabetes, malignancy, major bleeding (history or occurred during hospitalization). When more than two categories were present, dummy variables were introduced to define a reference group.

A p value < 0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with SAS system software, version 9.24.

RESULTS

Each site started patient enrollment after local IRB approval. Therefore, data were collected in different periods of consecutive 12 months in each site between August 2018 and December 2019. The study has been carried out in 76 cardiology centers [68 (89.5%) with a 24 hours/7 days primary PCI service and 19 (25.0%) with also a cardiac surgery onsite], well representing the Italian cardiology reality in terms of geographical distribution and level of hospital technology. Five-hundred-ninety-eight consecutive patients have been enrolled: 292 (48.8%) with AF at hospital admission and 306 (51.2%) developing AF during the index hospitalization. Among this latter group, 131 (42.8%) developed AF before and 175 (57.2%) after PCI; the median time from admission to AF onset was 18.0 (IQR 1.0-49.0) hours. Among the 211 patients with AF at admission and a history of AF, 116 (55.0%) had a permanent AF.

Baseline characteristics of the study population are shown in Table 1. The mean age of enrolled patients was 73±10 years, 70% were male, 33% diabetics and 26% had prior coronary revascularization. Patients with AF at admission presented more frequently a diagnosis of NSTE-ACS and were older, with a higher incidence of prior episodes of AF and major risk factors compared to patients developing AF during hospitalization (Table 1). The mean CHA_2DS_2-VASc was 4.1±1.5 and 3.6±1.5 (p=0.003), while the HAS-BLEED was 2.4±1.1 and 2.1±0.9 (p=0.02), in patients with AF at admission or developing AF during the hospitalization, respectively.

At the time of admission, 178 (29.8%) were receiving acetylsalicylic acid (ASA), 32 (5.4%) a DAPT and 210 (35%) an OAC (this latter more frequently used in patients with AF at admission compared to the other group) (Table 1).

Antithrombotic therapy in the peri-procedural period

A pretreatment with DAPT was employed in 345 (57.8%) patients, without differences between the two groups. Among the 210 patients on chronic OAC, it was interrupted before

PCI in 163 (77.6%).

Table 2 shows the angiographic and procedural variables of enrolled patients. A radial approach was used in 86%, a multivessel disease was present in 51%, and a drug-eluting stent (DES) was implanted in 98% of patients. A complete revascularization was obtained in 70% of cases.

In-hospital clinical events

The median duration of hospitalization in cardiology wards was 8 [IQR 5-12] days (7 [IQR 5-9] vs 9 [IQR 6-13] days for patients with AF at admission or new onset AF, respectively; p<0.0001). Among the 588 (98.3%) patients discharged alive, a sinus rhythm was present in 362 (61.6%) [106 (36.9%) with AF at admission and 256 (85.1%) new onset AF; p<0.0001]. In patients with new onset AF, the median duration of the arrhythmia was 4 (IQR 1.0-26.0) hours.

In-hospital clinical events are shown in Figure 1. An urgent revascularization occurred in 6.9%, a thromboembolic or major bleeding event in 3% and a definite stent thrombosis in 0.5% of cases, without differences between the two groups.

Antithrombotic therapies at discharge

The single antithrombotic compounds prescribed at discharge are shown in Figure 2.

A DAPT was prescribed in 26%, TAT in 65% and DAT in 9% of patients (Figure 3).

Among patients with AF at admission, TAT and DAT were more frequently prescribed compared to new onset AF patients (76.3% vs 53,8% and 12.5% vs 5.3%, respectively; both p<0.0001), while a DAPT was less often used (11.2% vs 39.5%; p<0.0001) (Figure 3).

DOACs were largely used in both patients receiving TAT (84.3%) and DAT (84.6%).

At multivariable analysis, history of major bleeding [odds ratio (OR): 5.40; 95% confidence intervals (CI): 2.42-12-05; p<0.0001] and malignancy (OR: 5.11; 95% CI: 1.77-14.78; p=0.0026) resulted the most important independent predictors of DAT prescription (Figure

4).

DISCUSSION

The major findings of this nationwide, contemporary, prospective registry of unselected ACS patients with concomitant AF undergoing PCI are the following: 1. AF at admission is associated with a high incidence of major risk factors while new onset AF more frequently develops after STEMI; 2. TAT is still the antithrombotic strategy of choice in AF patients undergoing PCI, especially in those with AF at admission, while DAT is reserved for patients deemed at high bleeding risk; 3. A quarter of patents did not receive any OAC and approximately 40% of patients with new onset AF has been discharged on DAPT.

It is estimated that one out of ten ACS patients requiring PCI with stent implantation may present AF prior to or occurring during the index hospitalization (1-3). In this latter group, the relative risk of developing AF is usually highest at the onset of ischemia, it diminishes over time and is higher in in those with greater clinical severity of ACS (22), as confirmed by our data. Despite its relatively frequent occurrence and the many etiologic factors involved in its pathogenetic condition, the short- or long-term prognostic significance of new-onset AF complicating ACS remains unclear (22-25). In our series of ACS patients treated with contemporary PCI strategies, as documented by the very high rates of transradial approach and DES implanted, new onset AF patients presented a slightly higher, not significant, rate of in-hospital events as compared to those with AF at admission. This finding can be related to the more frequent presence of STEMI and haemodynamic instability among patients developing AF during the index hospitalization.

The pharmacological management of patients with AF undergoing PCI requires a careful balance of the risk of thromboembolic and atherothrombotic events against the increased chance of bleeding, since most AF patients are likely to receive TAT for the prevention of stroke, stent thrombosis or recurrent cardiac events (26). In recent years, several randomized controlled trials including an overall population of more than 10,000 patients, assessed the safety of replacing TAT with DAT in AF patients treated with PCI (15-18,26). Meta-analyses of these trials showed that DAT is associated with reduced risk for major bleeding

compared with TAT, regardless of several features including clinical risk profile and PCI complexity (27,28). However, low-certainty evidence showed inconclusive effects of DAT versus TAT on risks for mortality, stroke and stent thrombosis (27,28).

The recent 2019 ACC/AHA/HRS guidelines for AF (29) recommend DAT with DOACs as an alternative to TAT to reduce bleeding, while, in the ESC guidelines released in 2016 (1), this indication is restricted to patients at baseline high bleeding risk. Based on the North American expert consensus document (7), the default approach is DAT, and short-term TAT can be considered in patients who have high thrombotic risk and low bleeding risk. Our data suggest that, although DOACs nearly replaced vitamin K antagonists, TAT is still largely used in contemporary clinical practice. This appears in accordance with the recent observation of an increased early stent thrombosis with DAT as compared to TAT with DOAC (30) supporting an initial course of TAT in all ACS patients with AF (31,32). On the other hand, as recommended by 2016 ESC guidelines on the management of AF (1) that did not consider all the evidence coming from recent trials, DAT was restricted to patients at high bleeding risk. These findings are consistent with previous nationwide registries or surveys conducted in Europe before the availability of newer evidence in this field (33,34), emphasizing the need for educational campaigns in order to translate recent evidence and guidelines recommendation into clinical practice.

The antithrombotic strategy is particularly challenging in patients who develop AF during an ACS episode, especially those with paroxysmal episodes of AF (22,35). Indeed, although it is unclear whether new onset AF associated with ACS has the same thromboembolic risk as a prior history of AF, substantial risk of AF recurrence following acute ischemia exists in these subjects (22). In this regard, a consensus document by the European Heart Rhythm Association (6) suggests that OAC should be generally prescribed in new onset AF, according to the individual risk of stroke, in combination with antiplatelet agents. In our registry, a quarter of the overall cohort was treated with DAPT and 40% of patients

developing AF during hospitalization was discharged without any OAC prescription, probably because the AF episode has been considered a transient epiphenomenon triggered by the acute myocardial ischemia. The low utilization of OAC in this population is consistent with a large Swedish registry (36) and other retrospective studies (37-39) on ACS. In a recent analysis of 149 patients developing AF during hospitalization for ACS and treated by PCI, DAT was strongly associated with mortality at long-term follow-up, suggesting that an intensified antithrombotic regimen should be considered also in this high-risk patient population (39). Studies specific to new-onset AF following ACS are needed in order to better identify those requiring anticoagulation and its optimal duration.

Study Limitations

Our study must be evaluated in the light of the known limitations of observational, cross-sectional studies. In addition, the data reported in the present analysis are limited to the time of hospitalization. However, a clinical follow-up at 6 months from enrolment is ongoing and will assess clinical outcomes and the adherence to prescribed antithrombotic strategy. Finally, even though the participating centers were asked to include in the registry all consecutive ACS patients with AF requiring coronary stents, we were not able to verify the enrolment process due to the absence of administrative auditing. However, based on the number of AF patients enrolled in previous nationwide registry of ACS, we believe that the rate of patients enrolled is reliable and it is unlikely that a selective enrolment in a few sites may have substantially changed the study results.

CONCLUSIONS

This nationwide registry provides unique insights into the current antithrombotic management of patients with ACS and concomitant AF undergoing coronary stenting. Although recent evidence showed the safety of DAT in this population, our data

demonstrate that TAT is still largely prescribed while DAT is reserved for patients deemed at high bleeding risk. At discharge, an OAC was not prescribed in 25% of the overall population and in 40% of patients developing AF during hospitalization.

Author contribution

The Steering Committee designed the study. All authors participated in the conduct of the study and contributed to the interpretation of the results. LDL drafted the manuscript. LG and DL analyzed the data. All authors read, revised and approved the final version of the article.

Technical appendix

Data can be accessed on request to Centro Studi ANMCO, Florence, Italy.

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Conflicts of interest

Dr. De Luca has received speakers honoraria from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer/BMS outside the submitted work; All other authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Gonzini and Lucci are employees of Heart Care

Foundation, which conducted the study with an unrestricted grant of research from Boehringer Ingelheim, Pharma GmbH & CoKG.

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FIGURE LEGENDS

Figure 1. In-hospital clinical events

Figure 2. Antithrombotic therapies prescribed at discharge

Figure 3 (Central illustration). Combination of antithrombotic therapies prescribed at discharge. DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; SAPT: single antiplatelet therapy; TAT: triple antithrombotic therapy

Figure 4. Independent predictors of DAT prescription at multivariable analysis

Table 1. Clinical characteristics, hemodynamic variables, laboratory parameters and antithrombotic therapy at baseline

	Overall (n=598)	**AF at admission (n=292)**	**New onset AF (n=306)**	**P value**
Age, yrs (mean±SD)	73±10	76±10	72±10	<0.0001
Males, n (%)	417 (69.7)	203 (69.5)	214 (69.9)	0.91
Body mass index	27.3±4.3	27.2±4.2	27.3±4.5	0.92
Final diagnosis, n (%) STEMI NSTE-ACS	 273 (45.7) 325 (54.3)	 101 (34.6) 191 (65.4)	 172 (56.2) 134 (43.8)	<0.0001
Clinical history and risk factors, n (%)				
Prior episodes of AF	253 (42.3)	211 (72.3)	42 (13.7)	<0.0001
Active smokers	119 (19.9)	46 (15.8)	73 (23.9)	0.01
Diabetes mellitus	198 (33.1)	109 (37.3)	89 (29.1)	0.03
Hypertension	467 (78.1)	245 (83.9)	222 (72.6)	0.0008
Hypercholesterolemia	310 (51.8)	155 (53.1)	155 (50.7)	0.55
Peripheral artery disease	51 (8.5)	33 (11.3)	18 (5.9)	0.02
Previous stroke/TIA	66 (11.0)	43 (14.7)	23 (7.5)	0.005
History of angina	177 (29.6)	114 (39.0)	63 (20.6)	<0.0001
History of heart failure	72 (12.0)	51 (17.5)	21 (6.9)	<0.0001
Previous MI	135 (22.6)	82 (28.1)	53 (17.3)	0.002
Prior PCI	143 (23.9)	87 (29.8)	56 (18.3)	0.001
Prior CABG	28 (4.7)	21 (7.2)	7 (2.3)	0.005
History of major bleeding	16 (2.7)	11 (3.8)	5 (1.6)	0.11

Chronic kidney disease	121 (20.2)	82 (28.1)	39 (12.8)	<0.0001
COPD	79 (13.2)	43 (14.7)	36 (11.8)	0.29
Cancer	23 (3.9)	15 (5.1)	8 (2.6)	0.11
Haemodynamic variables				
Killip III-IV, n (%)	76 (12.7)	27 (9.3)	49 (16.0)	0.13
Electrical instability, n (%)	55 (9.2)	14 (4.8)	41 (13.4)	0.0003
SBP, mmHg (mean±SD)	132±26	132±25	132±27	0.85
HR, bpm (mean±SD)	87±26	88±28	86±25	0.22
Ejection fraction, % (mean±SD)	46.8±10.4	47.0±10.3	46.5±10.4	0.56
Laboratory parameters, mean±SD				
Hemoglobin, g/dL	13.3±1.9	13.2±1.9	13.4±1.9	0.12
Creatinine, mg/dL	1.2±1.0	1.2±0.8	1.2±1.1	0.03
LDL Cholesterol, mg/dL	104±38	100±36	107±40	0.05
Tryglicerides, mg/dL	104 [78-144]	104 [78-148]	105 [77-140]	0.84
Platelets, 10^5/mL	223±82	211±76	235±86	0.0003
INR	1.3±0.6	1.4±0.7	1.1±0.2	<0.0001
Antithrombotic therapy, n (%)				
ASA only	146 (24.4)	66 (22.6)	80 (26.1)	0.31
P2Y12 inhibitors only	21 (3.5)	11 (3.8)	10 (3.3)	0.74
DAPT	32 (5.4)	14 (4.8)	18 (5.9)	0.55
LMWH	15 (2.5)	7 (2.4)	8 (2.6)	0.87
VKA	73 (12.2)	65 (22.3)	8 (2.6)	<0.0001
DOAC	137 (22.9)	119 (40.8)	18 (5.9)	<0.0001

Abbreviations: AF: atrial fibrillation; ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulants; HR: heart rate; INR: international normalized ratio; LDL: low density

lipoprotein; LMWH: low-molecular weight heparins; MI: myocardial infarction; NSTE-ACS: Non-ST elevation acute coronary syndromes; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: St-elevation myocardial infarction; TIA: transient ischemic attack; VKA: vitamin-K antagonists

Table 2. Angiographic and procedural variables and antithrombotic therapies administered in the cath lab.

	Overall (n=598)	**AF at admission (n=292)**	**New onset AF (n=306)**	**P value**
Radial approach, n (%)	517 (86.5)	260 (89.0)	257 (84.0)	0.07
Multivessel disease, n (%)	306 (51.2)	140 (48.0)	166 (54.3)	0.12
Basal TIMI 0/1, n (%)	226 (38.1)	88 (30.1)	138 (45.1)	<0.001
Site of PCI, n (%)				
Left main	44 (7.4)	19 (6.5)	25 (8.2)	0.44
Left anterior descending	326 (54.5)	155 (53.1)	171 (55.9)	0.49
Circumflex	176 (29.4)	82 (28.1)	94 (30.7)	0.48
Right coronary artery	229 (38.3)	116 (39.7)	113 (36.9)	0.48
Arterial/venous graft	9 (1.5)	7 (2.4)	2 (0.7)	0.08
Type of stent, n (%)				
BMS	15 (2.5)	9 (3.1)	6 (2.0)	0.38
DES, durable polymer	363 (60.7)	162 (55.5)	201 (65.7)	0.01
DES, biodegradable polymer	163 (27.3)	90 (30.8)	73 (23.9)	0.06
DES, polymer-free	78 (13.0)	47 (16.1)	31 (10.1)	0.03
>2 stents implanted, n (%)	115 (19.2)	53 (18.2)	62 (20.3)	0.51
Complete revascularization, n (%)	421 (70.4)	206 (70.6)	215 (70.3)	0.94
Antithrombotic therapies administered in the cath lab, n (%)				
ASA	31 (5.2)	20 (6.9)	11 (3.6)	0.07
DAPT	101 (16.9)	63 (21.6)	38 (12.4)	0.003
GP IIb/IIIa inhibitors	69 (11.5)	14 (4.8)	55 (18.0)	<0.0001
Cangrelor	9 (1.5)	$ (1.4)	5 (1.6)	0.23
Unfractionated heparin	333 (55.7)	187 (64.0)	146 (47.7)	<0.0001

Abbreviations: ASA: acetylsalicylic acid; BMS: bare metal stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; GP IIb/IIIa; glycoprotein IIb/IIIa receptor inhibitors; PCI: percutaneous coronary intervention

APPENDIX

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FIGURE 1

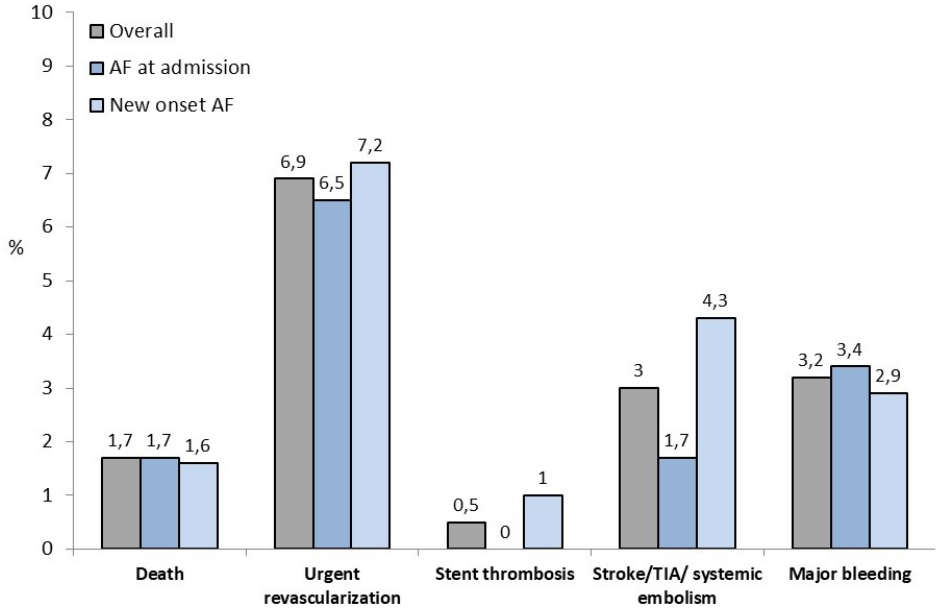

Figure 1

254x190mm (96 x 96 DPI)

FIGURE 2

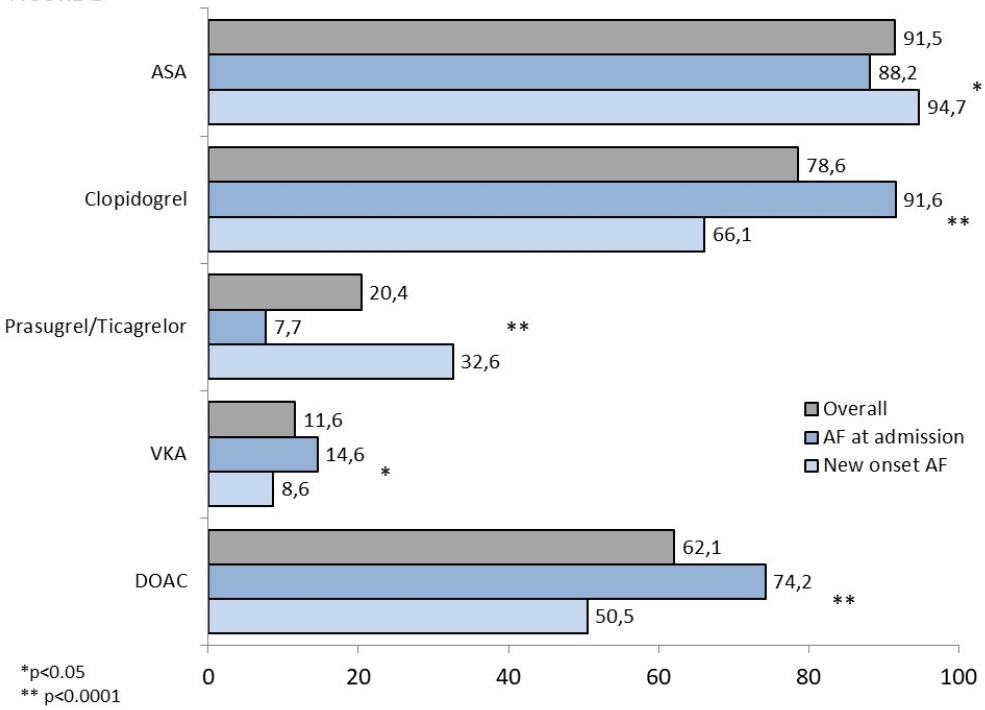

Figure 2

254x190mm (96 x 96 DPI)

FIGURE 3

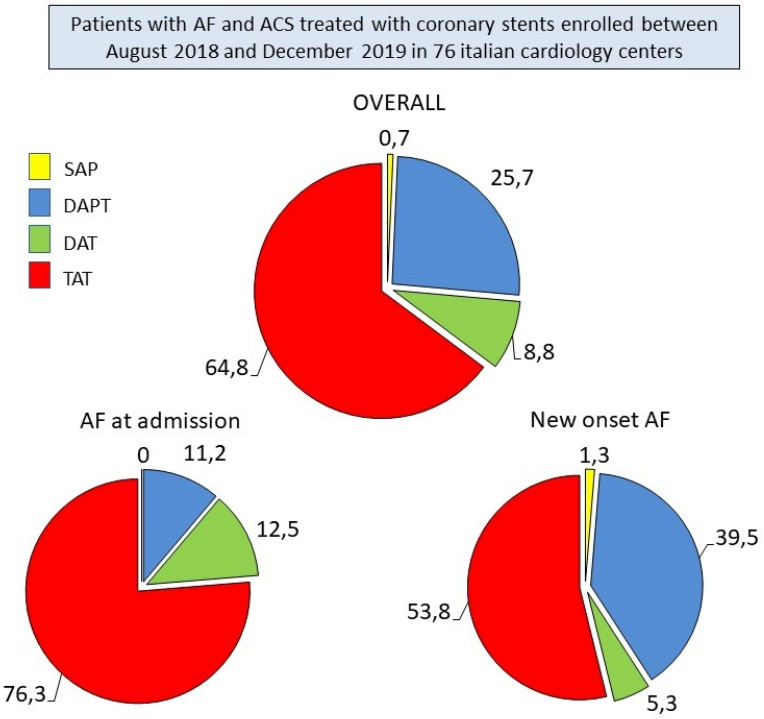

Figure 3

254x190mm (96 x 96 DPI)

FIGURE 4

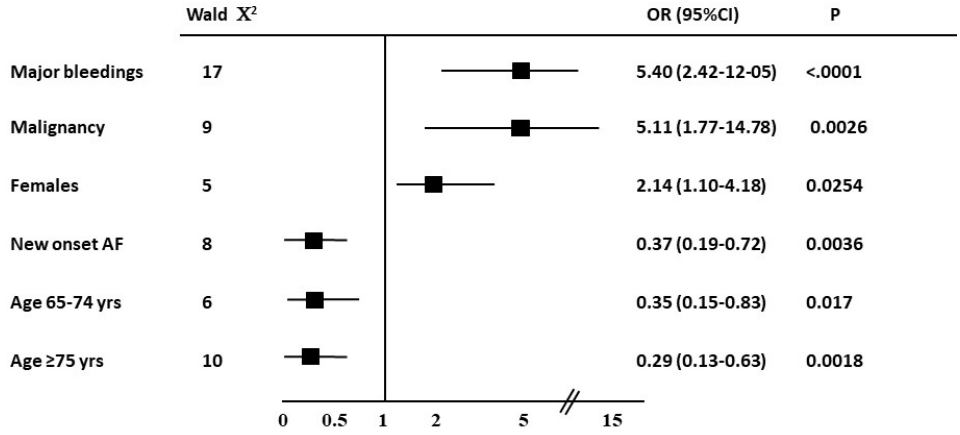

Figure 4

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5-6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6-7
Statistical methods	#12c	Explain how missing data were addressed	6-7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8
Participants	#13b	Give reasons for non-participation at each stage	n/a

Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8-9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

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Antithrombotic management of patients with acute coronary syndromes and atrial fibrillation undergoing coronary stenting: a prospective, observational, nationwide study

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Keywords:	Adult cardiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Cardiac Epidemiology < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

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Antithrombotic management of patients with acute coronary syndromes and atrial fibrillation undergoing coronary stenting: a prospective, observational, nationwide study

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*See Appendix for a complete list of centres and Investigators

Running title: MATADOR-PCI Study

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ABSTRACT

Objective. The aim of the study was to assess current management of patients with atrial fibrillation (AF) and acute coronary syndromes (ACS) undergoing coronary stenting.

Design. Non-interventional, prospective, nationwide study.

Setting. 76 private or public cardiology centers in Italy.

Participants. ACS patients with concomitant AF undergoing percutaneous coronary intervention (PCI).

Primary and secondary outcome measures. To obtain accurate and up-to-date information on pharmacological management of patients with AF admitted for an ACS and undergoing PCI with stent implantation.

Results. Over a 12-month period, 598 consecutive patients were enrolled: 48.8% with AF at hospital admission and 51.2% developing AF during hospitalization. At discharge, a triple antithrombotic therapy (TAT) was prescribed in 64.8%, dual antiplatelet therapy (DAPT) in 25.7%, and dual antithrombotic therapy (DAT) in 8.8% of patients. Among patients with AF at admission, TAT and DAT were more frequently prescribed compared to new onset AF patients (76.3% vs 53,8% and 12.5% vs 5.3%, respectively; both p<0.0001), while a DAPT was less often used (11.2% vs 39.5%; p<0.0001). At multivariable analysis, a major bleeding event [odds ratio (OR): 5.40; 95% confidence intervals (CI): 2.42-12-05; p<0.0001] and malignancy (OR: 5.11; 95% CI: 1.77-14.78; p=0.003) resulted the most important independent predictors of DAT prescription.

Conclusions. In this contemporary registry of ACS patients with AF treated with coronary stents, TAT still resulted as the antithrombotic strategy of choice, DAT was reserved for high bleeding risk and DAPT was mainly prescribed in those developing AF during hospitalization.

Key words: acute coronary syndromes; atrial fibrillation; percutaneous coronary intervention; stents; direct oral anticoagulants; treatment.

Strengths and limitations of this study

- Prospective, nationwide observational study
- Contemporary community-based registry evaluating the antithrombotic management of patients with ACS and AF undergoing PCI
- Data limited to the hospitalization period

INTRODUCTION

Approximately 10% of patients with acute coronary syndromes (ACS) requiring percutaneous coronary intervention (PCI) with stent implantation presents a concomitant atrial fibrillation (AF) (1-11). Such patients theoretically need oral anticoagulation (OAC) and dual antiplatelet therapy (DAPT), a combination known as triple antithrombotic therapy (TAT), in order to decrease both the risk of thromboembolism due to AF and the risk of thrombosis and recurrent ischemic events due to ACS and coronary stents (1-7). Unsurprisingly, TAT is associated with a high rate of major and fatal bleeding events (12). Recently, several randomized trials demonstrated the favorable safety profile of a double antithrombotic therapy (DAT), which combines OAC with a P2Y12 receptor inhibitor, as compared to TAT (13-17).

After the validation of these novel antithrombotic strategies and the dissemination of direct oral anticoagulants (DOACs) in clinical practice, no nationwide or community-based data describing contemporary pharmacological management of patients with AF and ACS treated with PCI are available. In this regard, the Italian National Association of Hospital Cardiologist (ANMCO) designed the MATADOR-PCI (Management of Antithrombotic TherApy in Patients with Chronic or DevelOping AtRial Fibrillation During Hospitalization for PCI) study, aimed to obtain accurate and up-to-date information concerning management and outcome of patients with AF admitted in cardiology intensive care units (CCUs) for an ACS undergoing PCI with stent implantation.

METHODS

The MATADOR-PCI was a prospective, observational, nationwide registry of consecutive patients with a confirmed diagnosis of ACS treated with PCI and concomitant AF conducted in Italy during a 1-year period.

All consecutive ACS patients [non-ST elevation-ACS (NSTE-ACS) or ST-elevation myocardial infarction (STEMI)] undergoing PCI and with AF at the time of hospital admission, either paroxysmal, persistent or permanent, or developing during the index hospitalization were included. Patients admitted with a diagnosis of ACS at the time of enrolment but not confirmed during hospitalization, ACS treated medically, with surgical revascularization or with percutaneous coronary balloon angioplasty without stent implantation, and those not giving informed consent were excluded from the survey.

ANMCO invited to participate in this study all Italian cardiology centers with a CCU and a catheterization laboratory performing at least 400 PCI per year (medium-high volume according to Italian standards), including university teaching hospitals, general and regional hospitals, and private clinics. No specific protocols or recommendations for evaluation, management, and/or treatment have been put forth during this observational study. However, current guidelines for the management of patients with AF, myocardial revascularization and ACS have been discussed during the investigator meetings.

Data collection and data quality

Data on demographics, cardiovascular and non-cardiovascular medical history, previous interventional procedures, type of ACS, type of AF, the timing of AF onset (if AF occurred during hospitalization), in-hospital management, pharmacological treatment, timing of PCI, severity and extension of coronary artery disease, number and type of stent, laboratory values, ECG characteristics, hemodynamic parameters, and in-hospital major clinical events were collected. Myocardial infarction was defined according to the third universal definition of MI (18). Stroke was identified as an acute neurologic deficit lasting >24 hours and affecting the ability to perform

daily activities with or without confirmation by imaging techniques. Stent thrombosis was defined according to the Academic Research Consortium (ARC) recommendations (19). Bleeding events were defined according to the Bleeding Academic Research Consortium (BARC) criteria (20). A major bleeding was defined as BARC ≥3.

At each site, the principal investigator was responsible for screening eligible consecutive patients. Data were collected using a web-based, electronic CRF with the central database located at the ANMCO Research Center. By using a validation plan, integrated in the data entry software, data were checked for missing or contradictory entries and values out of the normal range.

Patient consent and ethical approval

All patients were informed of the nature and aims of the study and asked to sign an informed consent for the anonymous management of their individual data. Local Institutional Review Boards (IRB) approved the study protocol according to the current Italian rules. The IRB of the coordinator center (A.O. San Camillo -Forlanini) approved the study on January 24th, 2018 (reference number: 151/CS).

The study was conducted in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines and the applicable local legislations of non-interventional studies. The MATADOR-PCI study is registered at ClinicalTrials.gov (NCT03656523).

Statistical analysis

Considering the explorative and observational nature of the study, no formal sample size calculation has been performed. However, considering the number of ACS patients with AF at the time of hospital admission or developing AF during the index hospitalization enrolled in previous snapshots performed in Italy and endorsed by ANMCO in the last 15 years (21), it was estimated to include approximately 500 patients (8% of ACS patients undergoing PCI in 1 year in about 100 centers) to allow for a representative national cohort in terms of geographical distribution and well balanced in terms of complexity (e.g. PCI volume,

cardiac surgery).

Normally distributed variables were expressed as mean ± standard deviation (SD), and compared using the Student t test, whereas non-normally distributed variables as median and interquartile range (IQR) and compared with the Mann-Whitney U test. Categorical variables were reported as numbers and percentages and compared using the chi-squared test or Fisher exact tests, as appropriate.

The study cohort was stratified according to the two pre-specified groups of patients: (1) those with AF at the time of hospital admission and (2) those developing AF after hospital admission for an ACS.

Clinically relevant variables which were significant at univariate analysis were included in a multivariable model (logistic regression) in order to identify the independent predictors of DAT and TAT prescription at discharge, compared to other antithrombotic strategies. The variables included in the logistic model for DAT were: age (<65 reference group, 65-74, ≥75 years), gender, onset of AF (at admission vs during hospitalization), type of ACS (STEMI vs NSTE-ACS), diabetes mellitus, malignancy, major bleeding (history or occurred during hospitalization). Variables included in the logistic model for TAT were the following: age (<65 reference group, 65-74, ≥75 years), gender, onset of AF (at admission vs during hospitalization), type of ACS (STEMI vs NSTE-ACS), : hypertension, history of HF, previous revascularization, prior AMI, stroke/TIA, malignancy, major bleeding (history or occurred during hospitalization). When more than two categories were present, dummy variables were introduced to define a reference group.

A p value < 0.05 was considered statistically significant. All tests were 2-sided. Analyses were performed with SAS system software, version 9.4.

RESULTS

Each site started patient enrollment after local IRB approval. Therefore, data were collected in different periods of consecutive 12 months in each site between August 2018 and December 2019. The study has been carried out in 76 cardiology centers [68 (89.5%) with a 24 hours/7 days primary PCI service and 19 (25.0%) with also a cardiac surgery onsite], well representing the Italian cardiology reality in terms of geographical distribution and level of hospital technology. Five-hundred-ninety-eight consecutive patients have been enrolled: 292 (48.8%) with AF at hospital admission and 306 (51.2%) developing AF during the index hospitalization. Among this latter group, 131 (42.8%) developed AF before and 175 (57.2%) after PCI; the median time from admission to AF onset was 18.0 (IQR 1.0-49.0) hours. Among the 211 patients with AF at admission and a history of AF, 116 (55.0%) had a permanent AF.

Baseline characteristics of the study population are shown in Table 1. The mean age of enrolled patients was 73±10 years, 70% were male, 33% diabetics and 26% had prior coronary revascularization. Patients with AF at admission presented more frequently a diagnosis of NSTE-ACS and were older, with a higher incidence of prior episodes of AF and major risk factors compared to patients developing AF during hospitalization (Table 1). The mean CHA_2DS_2-VASc was 3.7±1.6 and 2.9±1.7 ($p<0.0001$), while the HAS-BLEED was 2.6±1.1 and 2.1±1.1 ($p<0.0001$), in patients with AF at admission or developing AF during the hospitalization, respectively.

At the time of admission, 178 (29.8%) were receiving acetylsalicylic acid (ASA), 32 (5.4%) a DAPT and 210 (35%) an OAC (this latter more frequently used in patients with AF at admission compared to the other group) (Table 1).

Antithrombotic therapy in the peri-procedural period

A pretreatment with DAPT was employed in 345 (57.8%) patients, without differences between the two groups. Among the 210 patients on chronic OAC, it was interrupted before

PCI in 163 (77.6%).

Table 2 shows the angiographic and procedural variables of enrolled patients. A radial approach was used in 86%, a multivessel disease was present in 51%, and a drug-eluting stent (DES) was implanted in 98% of patients. A complete revascularization was obtained in 70% of cases.

In-hospital clinical events

The median duration of hospitalization in cardiology wards was 8 [IQR 5-12] days (7 [IQR 5-9] vs 9 [IQR 6-13] days for patients with AF at admission or new onset AF, respectively; p<0.0001). Ten (1.7%) patients died during the hospitalization (5 with AF at admission and 5 with new onset AF). Among the remaining 588 (98.3%) patients discharged alive, a sinus rhythm was present in 362 (61.6%) [106 (36.9%) with AF at admission and 256 (85.1%) new onset AF; p<0.0001]. In patients with new onset AF, the median duration of the arrhythmia was 4 (IQR 1.0-26.0) hours and an electrical cardioversion was performed in 28 (9.2%).

In-hospital clinical events are shown in Figure 1. An urgent revascularization occurred in 6.9%, a thromboembolic or major bleeding event in 3% and a definite stent thrombosis in 0.5% of cases, without differences between the two groups.

Antithrombotic therapies at discharge

The single antithrombotic compounds prescribed at discharge are shown in Figure 2.

A DAPT was prescribed in 26%, TAT in 65% and DAT in 9% of patients (Figure 3).

Among patients with AF at admission, TAT and DAT were more frequently prescribed compared to new onset AF patients (76.3% vs 53,8% and 12.5% vs 5.3%, respectively; both p<0.0001), while a DAPT was less often used (11.2% vs 39.5%; p<0.0001) (Figure 3).

DOACs were largely used in both patients receiving TAT (84.3%) and DAT (84.6%).

At multivariable analysis, a major bleeding event [odds ratio (OR): 5.40; 95% confidence

intervals (CI): 2.42-12-05; p<0.0001] and malignancy (OR: 5.11; 95% CI: 1.77-14.78; p=0.003) resulted the most important independent predictors of DAT prescription (Figure 4). The independent predictors of TAT prescription derived from multivariable analysis are shown in supplementary Table 1.

DISCUSSION

The major findings of this nationwide, contemporary, prospective registry of unselected ACS patients with concomitant AF undergoing PCI are the following: 1. AF at admission is associated with a high incidence of major risk factors while new onset AF more frequently develops after STEMI; 2. TAT is still the antithrombotic strategy of choice in AF patients undergoing PCI, especially in those with AF at admission, while DAT is reserved for patients deemed at high bleeding risk; 3. A quarter of patents did not receive any OAC and approximately 40% of patients with new onset AF has been discharged on DAPT.

It is estimated that one out of ten ACS patients requiring PCI with stent implantation may present AF prior to or occurring during the index hospitalization (1-3). In this latter group, the relative risk of developing AF is usually highest at the onset of ischemia, it diminishes over time and is higher in in those with greater clinical severity of ACS (22), as confirmed by our data. Despite its relatively frequent occurrence and the many etiologic factors involved in its pathogenetic condition, the short- or long-term prognostic significance of new-onset AF complicating ACS remains unclear (22-25). In our series of ACS patients treated with contemporary PCI strategies, as documented by the very high rates of transradial approach and DES implanted, new onset AF patients presented a slightly higher, not significant, rate of in-hospital ischemic events as compared to those with AF at admission. This finding can be related to the more frequent presence of STEMI and haemodynamic instability among patients developing AF during the index hospitalization. Indeed, new-onset atrial fibrillation occurs more frequently in critically unwell patients and its incidence increases with greater severity of illness (26,27).

The pharmacological management of patients with AF undergoing PCI requires a careful balance of the risk of thromboembolic and atherothrombotic events against the increased chance of bleeding, since most AF patients are likely to receive TAT for the prevention of stroke, stent thrombosis or recurrent cardiac events (28). In recent years, several randomized controlled trials including an overall population of more than 10,000 patients, assessed the

safety of replacing TAT with DAT in AF patients treated with PCI (15-18,28). Meta-analyses of these trials showed that DAT is associated with reduced risk for major bleeding compared with TAT, regardless of several features including clinical risk profile and PCI complexity (29,30). However, low-certainty evidence showed inconclusive effects of DAT versus TAT on risks for mortality, stroke and stent thrombosis (29,30).

The recent 2019 ACC/AHA/HRS guidelines for AF (31) recommended DAT with DOACs as an alternative to TAT to reduce bleeding, while, in the ESC guidelines released in 2016 (1), this indication was restricted to patients at baseline high bleeding risk. Based on the North American expert consensus document (7), the default approach was DAT, and short-term TAT could be considered in patients who have high thrombotic risk and low bleeding risk. Accordingly, recent 2020 ESC guidelines on the management of AF recommend early cessation (≤1 week) of aspirin and continuation of DAT for up to 12 months in AF patients with ACS undergoing an uncomplicated PCI if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis (32). This appears in accordance with the recent observation of an increased early stent thrombosis with DAT as compared to TAT with DOAC (33) supporting an initial course of TAT in all ACS patients with AF (34,35). Our data suggest that, although DOACs nearly replaced vitamin K antagonists, TAT is still largely used in contemporary clinical practice. These findings may be related to 2016 ESC guidelines recommendations (1) that were available during the conduction of our registry and did not consider all the evidence coming from recent trials, to the lack of hospital protocols updating or to the issues in changing therapeutic habits, as confirmed by previous nationwide surveysconducted in Europe before the availability of newer evidence in this field (36,37). All these data emphasize the need for educational campaigns in order to translate recent evidence and guidelines recommendation into clinical practice.

The antithrombotic strategy is particularly challenging in patients who develop AF during an ACS episode, especially those with paroxysmal episodes of AF (22,38). Indeed, although it

is unclear whether new onset AF associated with ACS has the same thromboembolic risk as a prior history of AF, substantial risk of AF recurrence following acute ischemia exists in these subjects (22). In this regard, a consensus document by the European Heart Rhythm Association (6) suggests that OAC should be generally prescribed in new onset AF, according to the individual risk of stroke, in combination with antiplatelet agents. In our registry, a quarter of the overall cohort was treated with DAPT and 40% of patients developing AF during hospitalization was discharged without any OAC prescription, probably because the AF episode has been considered a transient epiphenomenon triggered by the acute myocardial ischemia. The high prescription of DAPT and the concomitant low use of OAT could justify the greater prescription of potent oral P2Y12 inhibitors observed in our cohort of patients with new onset AF compared to those with AF at admission. The low utilization of OAC in this population is consistent with large retrospective analyses of critically ill patients with sepsis (39,40) and a Swedish registry (41) and other retrospective studies (42-44) on ACS. In a recent analysis of 149 patients developing AF during hospitalization for ACS and treated by PCI, DAT was strongly associated with mortality at long-term follow-up, suggesting that an intensified antithrombotic regimen should be considered also in this high-risk patient population (44). Studies specific to new-onset AF following ACS are needed in order to better identify those requiring anticoagulation and its optimal duration.

Study Limitations

Our study must be evaluated in the light of the known limitations of observational, cross-sectional studies. In addition, the data reported in the present analysis are limited to the time of hospitalization. However, a clinical follow-up at 6 months from enrolment is ongoing and will assess clinical outcomes and the adherence to prescribed antithrombotic strategy. Finally, even though the participating centers were asked to include in the registry all consecutive ACS patients with AF requiring coronary stents, we were not able to verify the enrolment process due to the

absence of administrative auditing. However, based on the number of AF patients enrolled in previous nationwide registry of ACS, we believe that the rate of patients enrolled is reliable and it is unlikely that a selective enrolment in a few sites may have substantially changed the study results.

CONCLUSIONS

This nationwide registry provides unique insights into the current antithrombotic management of patients with ACS and concomitant AF undergoing coronary stenting. Although recent evidence showed the safety of DAT in this population, our data demonstrate that TAT is still largely prescribed while DAT is reserved for patients deemed at high bleeding risk. At discharge, an OAC was not prescribed in 25% of the overall population and in 40% of patients developing AF during hospitalization.

Author contribution

The Steering Committee designed the study. All authors participated in the conduct of the study and contributed to the interpretation of the results. LDL, DG, ADL and MMG drafted, planned and conducted the manuscript. LG and DL analyzed the data. AR, LB, SU, AM, FSU, FF, FL and PC read, revised and approved the final version of the article. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Data are available upon reasonable request to ANMCO Research Center, Florence, Italy.

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The sponsor of the study was the Heart Care Foundation, a non-profit independent organization, which also owns the database. Database management, quality control of the data and data analyses were under the responsibility of the ANMCO Research Centre of the Heart Care Foundation. The study was partially supported by an unrestricted grant by Boehringer Ingelheim, Pharma GmbH & CoKG. No compensations were provided to participating sites, investigators, nor members of the Steering Committee. The Steering Committee of the study had full access to all the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

Dr. De Luca has received speakers honoraria from Bayer, Boehringer Ingelheim, Daiichi Sankyo, Pfizer/BMS outside the submitted work; All other authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or

services may be discussed in this article. Gonzini and Lucci are employees of Heart Care Foundation, which conducted the study with an unrestricted grant of research from Boehringer Ingelheim, Pharma GmbH & CoKG.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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FIGURE LEGENDS

Figure 1. In-hospital clinical events

Figure 2. Antithrombotic therapies prescribed at discharge

Figure 3 (Central illustration). Combination of antithrombotic therapies prescribed at discharge. DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; SAPT: single antiplatelet therapy; TAT: triple antithrombotic therapy

Figure 4. Independent predictors of DAT prescription at multivariable analysis

Table 1. Clinical characteristics, hemodynamic variables, laboratory parameters and antithrombotic therapy at baseline

	Overall (n=598)	**AF at admission (n=292)**	**New onset AF (n=306)**	**P value**
Age, yrs (mean±SD)	73±10	76±10	72±10	<0.0001
Males, n (%)	417 (69.7)	203 (69.5)	214 (69.9)	0.91
Body mass index, Kg/m^2 (mean±SD)	27.3±4.3	27.2±4.2	27.3±4.5	0.92
Final diagnosis, n (%)				<0.0001
STEMI	273 (45.7)	101 (34.6)	172 (56.2)	
NSTE-ACS	325 (54.3)	191 (65.4)	134 (43.8)	
Clinical history and risk factors, n (%)				
Prior episodes of AF	253 (42.3)	211 (72.3)	42 (13.7)	<0.0001
Active smokers	119 (19.9)	46 (15.8)	73 (23.9)	0.01
Diabetes mellitus	198 (33.1)	109 (37.3)	89 (29.1)	0.03
Hypertension	467 (78.1)	245 (83.9)	222 (72.6)	0.0008
Hypercholesterolemia	310 (51.8)	155 (53.1)	155 (50.7)	0.55
Peripheral artery disease	51 (8.5)	33 (11.3)	18 (5.9)	0.02
Previous stroke/TIA	66 (11.0)	43 (14.7)	23 (7.5)	0.005
History of angina	177 (29.6)	114 (39.0)	63 (20.6)	<0.0001
History of heart failure	72 (12.0)	51 (17.5)	21 (6.9)	<0.0001
Previous MI	135 (22.6)	82 (28.1)	53 (17.3)	0.002
Prior PCI	143 (23.9)	87 (29.8)	56 (18.3)	0.001
Prior CABG	28 (4.7)	21 (7.2)	7 (2.3)	0.005
History of major bleeding	16 (2.7)	11 (3.8)	5 (1.6)	0.11
Chronic kidney disease	121 (20.2)	82 (28.1)	39 (12.8)	<0.0001
COPD	79 (13.2)	43 (14.7)	36 (11.8)	0.29
Cancer	23 (3.9)	15 (5.1)	8 (2.6)	0.11
Haemodynamic variables				
Killip III-IV, n (%)	76 (12.7)	27 (9.3)	49 (16.0)	0.13
Electrical instability, n (%)	55 (9.2)	14 (4.8)	41 (13.4)	0.0003

SBP, mmHg (mean±SD)	132±26	132±25	132±27	0.85
HR, bpm (mean±SD)	87±26	88±28	86±25	0.22
Ejection fraction, % (mean±SD)	46.8±10.4	47.0±10.3	46.5±10.4	0.56
Laboratory parameters				
Hemoglobin, g/dL, (mean±SD)	13.3±1.9	13.2±1.9	13.4±1.9	0.12
Creatinine, mg/dL, (mean±SD)	1.2±1.0	1.2±0.8	1.2±1.1	0.03
LDL Cholesterol, mg/dL, (mean±SD)	104±38	100±36	107±40	0.05
Tryglicerides, mg/dL, (median [IQR])	104 [78-144]	104 [78-148]	105 [77-140]	0.84
Platelets, 10^5/mL, (mean±SD)	223±82	211±76	235±86	0.0003
INR, (mean±SD)	1.3±0.6	1.4±0.7	1.1±0.2	<0.0001
Antithrombotic therapy, n (%)				
ASA only	146 (24.4)	66 (22.6)	80 (26.1)	0.31
P2Y12 inhibitors only	21 (3.5)	11 (3.8)	10 (3.3)	0.74
DAPT	32 (5.4)	14 (4.8)	18 (5.9)	0.55
LMWH	15 (2.5)	7 (2.4)	8 (2.6)	0.87
VKA	73 (12.2)	65 (22.3)	8 (2.6)	<0.0001
DOAC	137 (22.9)	119 (40.8)	18 (5.9)	<0.0001

Abbreviations: AF: atrial fibrillation; ASA: acetylsalicylic acid; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; DAPT: dual antiplatelet therapy; DOAC: direct oral anticoagulants; HR: heart rate; INR: international normalized ratio; LDL: low density lipoprotein; LMWH: low-molecular weight heparins; MI: myocardial infarction; NSTE-ACS: Non-ST elevation acute coronary syndromes; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; STEMI: St-elevation myocardial infarction; TIA: transient ischemic attack; VKA: vitamin-K antagonists

Table 2. Angiographic and procedural variables and antithrombotic therapies administered in the cath lab.

	Overall (n=598)	**AF at admission (n=292)**	**New onset AF (n=306)**	**P value**
Radial approach, n (%)	517 (86.5)	260 (89.0)	257 (84.0)	0.07
Multivessel disease, n (%)	306 (51.2)	140 (48.0)	166 (54.3)	0.12
Basal TIMI 0/1, n (%)	226 (38.1)	88 (30.1)	138 (45.1)	<0.001
Site of PCI, n (%)				
Left main	44 (7.4)	19 (6.5)	25 (8.2)	0.44
Left anterior descending	326 (54.5)	155 (53.1)	171 (55.9)	0.49
Circumflex	176 (29.4)	82 (28.1)	94 (30.7)	0.48
Right coronary artery	229 (38.3)	116 (39.7)	113 (36.9)	0.48
Arterial/venous graft	9 (1.5)	7 (2.4)	2 (0.7)	0.08
Type of stent, n (%)				
BMS	15 (2.5)	9 (3.1)	6 (2.0)	0.38
DES, durable polymer	363 (60.7)	162 (55.5)	201 (65.7)	0.01
DES, biodegradable polymer	163 (27.3)	90 (30.8)	73 (23.9)	0.06
DES, polymer-free	78 (13.0)	47 (16.1)	31 (10.1)	0.03
>2 stents implanted, n (%)	115 (19.2)	53 (18.2)	62 (20.3)	0.51
Complete revascularization, n (%)	421 (70.4)	206 (70.6)	215 (70.3)	0.94
Antithrombotic therapies administered in the cath lab, n (%)				
ASA	31 (5.2)	20 (6.9)	11 (3.6)	0.07
DAPT	101 (16.9)	63 (21.6)	38 (12.4)	0.003
GP IIb/IIIa inhibitors	69 (11.5)	14 (4.8)	55 (18.0)	<0.0001
Cangrelor	9 (1.5)	$ (1.4)	5 (1.6)	0.23
Unfractionated heparin	333 (55.7)	187 (64.0)	146 (47.7)	<0.0001

Abbreviations: ASA: acetylsalicylic acid; BMS: bare metal stent; DAPT: dual antiplatelet therapy; DES: drug-eluting stent; GP IIb/IIIa; glycoprotein IIb/IIIa receptor inhibitors; PCI: percutaneous coronary intervention.

Group Names

ANMCO: Associazione Nazionale Medici Cardiologi Ospedalieri

FIGURE 1

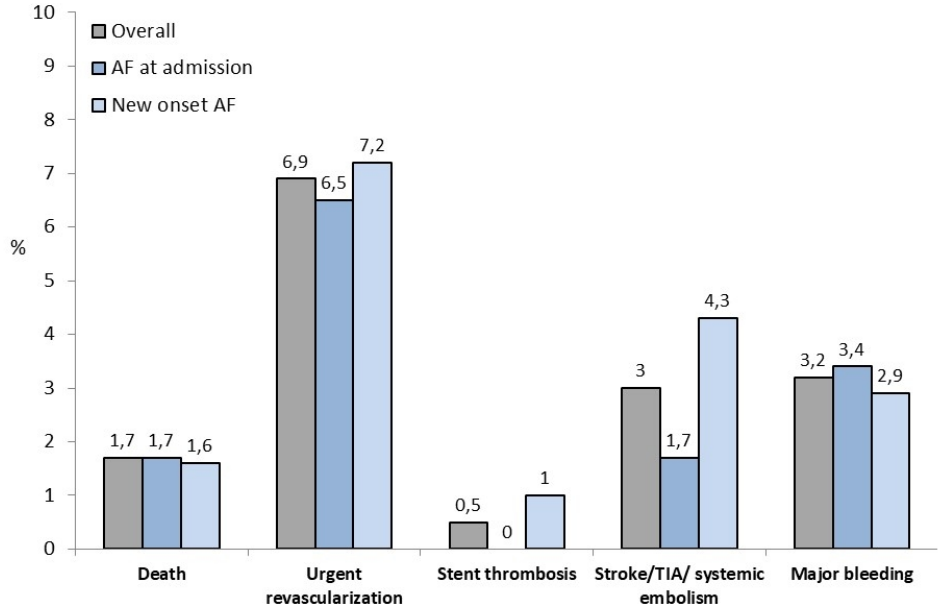

Figure 1

254x190mm (96 x 96 DPI)

FIGURE 2

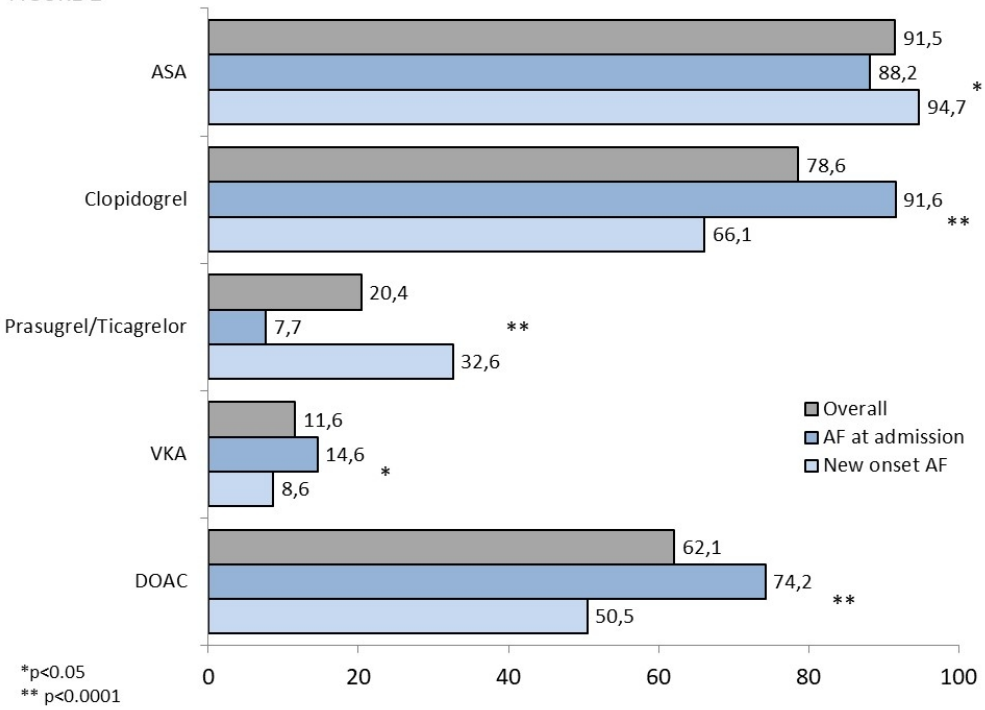

Figure 2

254x190mm (96 x 96 DPI)

FIGURE 3

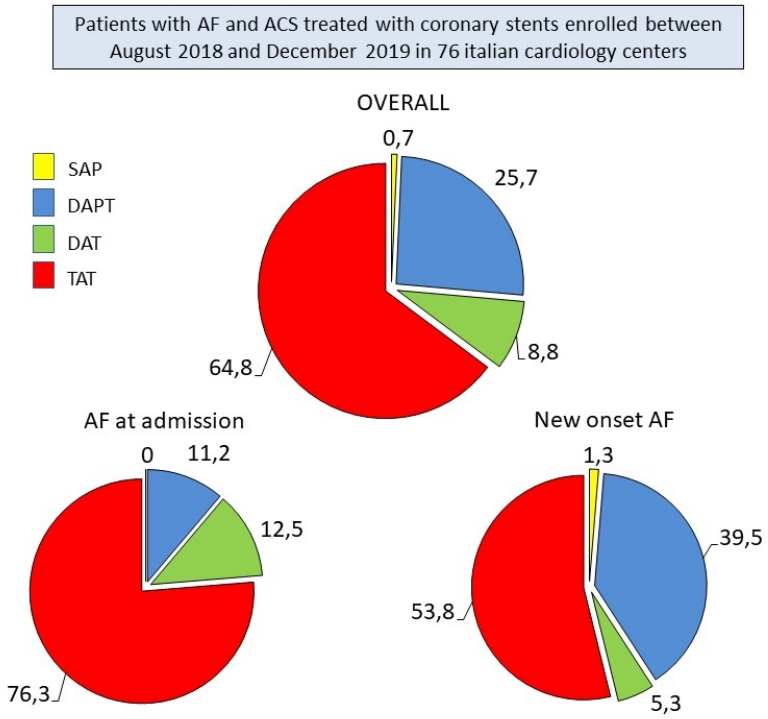

Figure 3

254x190mm (96 x 96 DPI)

FIGURE 4

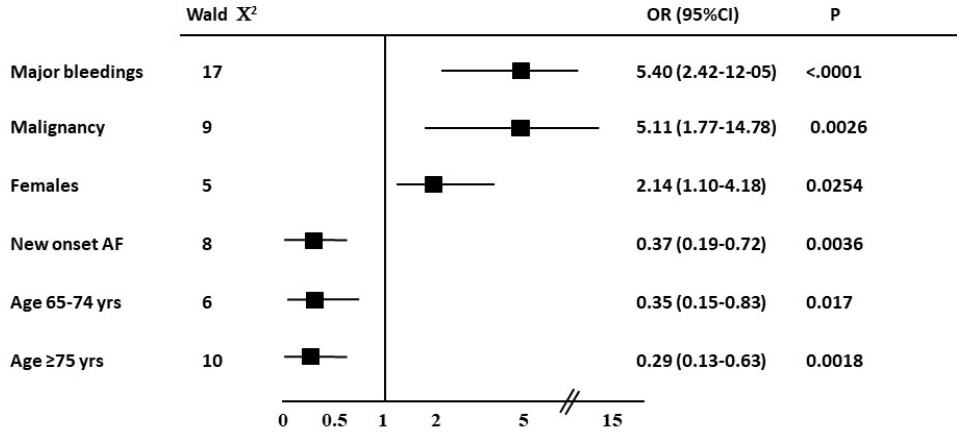

Figure 4

254x190mm (96 x 96 DPI)

APPENDIX

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TABLE 1 SUPPL. Independent predictors of TAT prescription at discharge.

Variable	Odds Ratio	95% Confidence Intervals	P value
Age 65-74 vs <65 years	2.87	1.69-4.87	0.0003
Age ≥75 vs <65 years	2.32	1.40-3.82	0.0003
New onset AF	0.42	0.29-0.63	<0.0001
Malignancy	0.31	0.12-0.81	0.002
Bleeding events	0.21	0.10-0.43	<0.0001

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5-6
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	6

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	6-7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	6-7
Statistical methods	#12c	Explain how missing data were addressed	6-7
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	N/A
Statistical methods	#12e	Describe any sensitivity analyses	N/A
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8
Participants	#13b	Give reasons for non-participation at each stage	n/a

Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8-9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
Main results	#16b	Report category boundaries when continuous variables were categorized	9
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalisability	#21	Discuss the generalisability (external validity) of the study results	11-12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15