Relation of Atrial Fibrillation to Angiographic Characteristics and Coronary Artery Disease Severity in Patients Undergoing Percutaneous Coronary Intervention

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Patients with atrial fibrillation (AF) have an increased risk of coronary artery disease (CAD) compared to patients without. Angiographic characteristics, clinical presentation and severity of CAD according to the presence of AF have been poorly described. We performed a retrospective study of 303 consecutive patients (mean age 69.6 ± 10.8 years; 23.1% women) with and without AF undergoing percutaneous coronary intervention. Data on (1) type of CAD presentation, (2) coronary involvement, and (3) number of diseased coronary vessels (≥70%/luminal narrowing) were collected. CHA_2DS_2-VASc and 2 major adverse cardiac event (MACE) scores were calculated. Presentation of CAD was ST-segment elevation myocardial infarction (STEMI) in 37.6% of patients, non−STEMI-unstable angina in 55.1%, and other in 7.3%. Non−STEMI-unstable angina was more common in AF (69.6% vs 46.6%, p <0.001), while STEMI was more in the non-AF (22.3% vs 46.6%, p <0.001) group. Left anterior descending artery (LAD) was the most common diseased vessel (70.6%) followed by right coronary artery (RCA, 56.4%) and obtuse marginal artery (36.6%). Patients with AF had a significantly lower RCA involvement (47.3% vs 61.8%, p = 0.016), with a trend for LAD (64.3% vs 74.3%, p = 0.069). At multivariable logistic regression analysis, AF remained inversely associated with RCA involvement (odds ratio [OR] 0.541, 95% confidence interval [CI] 0.335 to 0.874, p = 0.012) and with ≥3 vessel CAD (OR 0.470, 95% CI 0.272 to 0.810, p = 0.007). The 2MACE score was associated with diseased LAD (OR 1.301, 95% CI 1.103 to 1.535, p = 0.002) and with ≥3 vessel CAD (OR 1.330, 95% CI 1.330 to 1.140, p <0.001). In conclusion, patients with AF show lower RCA involvement and generally less severe CAD compared to non-AF ones. The 2MACE score was higher in LAD obstruction and identified patients with severe CAD.
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The clinical course of atrial fibrillation (AF) may be complicated by a variety of ischemic events including thromboembolism and cardiovascular disease.[1] Previous studies showed that AF patients have an increased risk of coronary artery disease (CAD) compared to patients without.[2] Oral anticoagulation seems to only have a marginal effect on the incidence of cardiovascular complications in AF.[3] Furthermore, the efficacy of warfarin therapy for the prevention of major adverse cardiac events (MACE) depends on the quality of anticoagulation control. Thus, AF patients treated with warfarin but with suboptimal time in therapeutic range (<70%) still experience a high rate of MACE.[4] Despite optimal thromboprophylaxis, AF patients still have a residual cardiovascular risk, and nearly half of deaths are currently related to cardiovascular causes.[5,6] A gap of knowledge in this field is represented by the limited characterization of angiographic features and clinical presentation of CAD in patients according to the presence of AF, which have been poorly described. We performed a retrospective cohort study including consecutive patients undergoing percutaneous coronary intervention (PCI) to describe: (1) clinical presentation of CAD; and (2) type and number of diseased coronary vessels angiography differences and between patients with and without AF.

Methods

Retrospective cohort study including patients undergoing PCI at the Department of Clinical Internal, Anesthesiologic, and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy. Within the Department, patients were recruited from 2 centers, of which one is primarily dedicated to the monitoring of anticoagulation therapies and

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managing most patients with AF referring to the hospital. At baseline, the following data were collected: anthropometric data, concomitant drugs, comorbidities, type of CAD presentation, and number of diseased coronary vessels. The type of CAD presentation was divided into 3 groups (1) non−ST-segment elevation myocardial infarction (NSTEMI)-unstable angina (UA), (2) ST-segment elevation MI (STEMI), (3) others including: stable angina, positive noninvasive functional test, preoperative evaluation. Cardiovascular risk factors were defined according to international definitions; the diagnosis of AF was confirmed by ECG showing the presence of AF, or from medical records in patients with paroxysmal AF. Exclusion criteria: age <18 years; presence of myocardial infarction with non-obstructive CAD, active cancer, chronic infectious or autoimmune disease. At baseline for each patient the CHA_2DS_2-VASc and 2MACE score were calculated to assess the thromboembolic and cardiovascular risk, respectively.[7] The 2MACE score[7] includes 2 points for Metabolic Syndrome and Age ≥75, 1 point for MI/revascularization, Congestive heart failure (ejection fraction ≤40 %), thrombo-embolism (stroke and/or transient ischemic attack), ranging from 0 to 7 points.[7] Patients were classified at "high cardiovascular risk" if the 2MACE score was ≥3.

During invasive coronary angiography data on left anterior descending artery (LAD), left circumflex artery (LCX), left main coronary artery, obtuse marginal artery (OM) and right coronary artery (RCA) were collected. Severe obstructive atherosclerotic CAD was assessed by presence of previous PCI or surgical coronary revascularization, and/or 1 or more angiographically documented coronary stenosis. A coronary vessel was considered as diseased for a ≥70% luminal narrowing, based on previous finding showing that in the majority of cases this stenosis is hemodynamically significant.[8]

Categorical variables were reported as counts and percentage. Continuous variables were expressed as mean and standard deviation and compared by Student t test. The Fisher exact test was used to compare proportions. A first descriptive analysis according to presence of AF was performed. Then, a multivariable logistic regression analysis was used to investigated factors associated with LAD or RCA involvement or to severe multivessel CAD. In the multivariable model, only variables with a p value <0.100 at univariable analysis were included. Only p values <0.05 were considered as statistically significant. All tests were 2-tailed and analyses were performed using computer software packages (SPSS-25, SPSS Inc. and MedCalc Software Ltd).

Results

Seven patients were excluded as they presented with nonobstructive CAD. Overall, 112 patients had AF, of whom 51 (45.5%) had paroxysmal AF. Table 1 reports characteristic of patients with and without AF. Patients with AF were older, more frequently women, with a higher prevalence of arterial hypertension, COPD and previous thromboembolism (Table 1). Regarding treatments, a higher use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blocker (ARBs), oral anticoagulants, proton pump inhibitors, was found in AF patients, while a higher use of antiplatelet drugs was present in non-AF patients (Table 1). Similar results were found in the subgroup of patients without previous ischemic heart disease at baseline (not shown). Overall, 37.6% of patient presentations of CAD were STEMI, in 55.1% were NSTEMI-UA, and 7.3% others. The proportion of NSTEMI-UA was higher in AF than non-AF patients 69.6% versus 46.6%, p <0.001 (Figure 1). Conversely, a

Table 1
Characteristics of study population according to the presence of atrial fibrillation

	Whole cohort (n= 303)	Atrial fibrillation		p
		No (n=191)	Yes (n=112)	
Age (years)	69.6±10.8	66.6±11.4	74.2±7.6	<0.001
Age ≥ 75 years	111 (36.6%)	54 (28.3%)	57 (50.9%)	<0.001
Women	70 (23.1%)	37 (19.6%)	33 (28.9%)	0.068
Arterial hypertension	266 (87.8%)	159 (84.1%)	107 (93.9%)	0.012
Diabetes	87 (28.7%)	55 (29.1%)	32 (28.1%)	0.896
Chronic obstructive pulmonary disease	63 (20.8%)	29 (15.3%)	34 (29.8%)	0.003
Previous ischemic heart disease	109 (36.0%)	62 (32.8%)	47 (41.2%)	0.174
Heart failure	77 (25.4%)	43 (22.8%)	34 (29.8%)	0.176
Previous Thromboembolism	28 (9.2%)	12 (6.3%)	16 (14.0%)	0.039
CHA_2DS_2-VASc score	2.98±1.69	2.59±1.68	3.62±1.49	<0.001
2MACE score	2.69±1.69	2.46±1.64	3.05±1.71	0.003
Concomitant drugs				
Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers	184 (60.7%)	99 (52.4%)	85 (74.6%)	<0.001
Oral anticoagulants	97 (32.0%)	6 (3.2%)	91 (79.8%)	<0.001
Proton pump inhibitors	134 (44.2%)	67 (35.4%)	67 (58.8%)	<0.001
Antiplatelet drugs	124 (40.9%)	92 (48.7%)	32 (28.1%)	<0.001
β-Blockers	119 (39.3%)	70 (37.0%)	49 (43.0%)	0.332
Calcium channel blockers	78 (25.7%)	46 (24.3%)	32 (28.1%)	0.499
Statins	156 (51.5%)	92 (48.7%)	64 (56.1%)	0.236

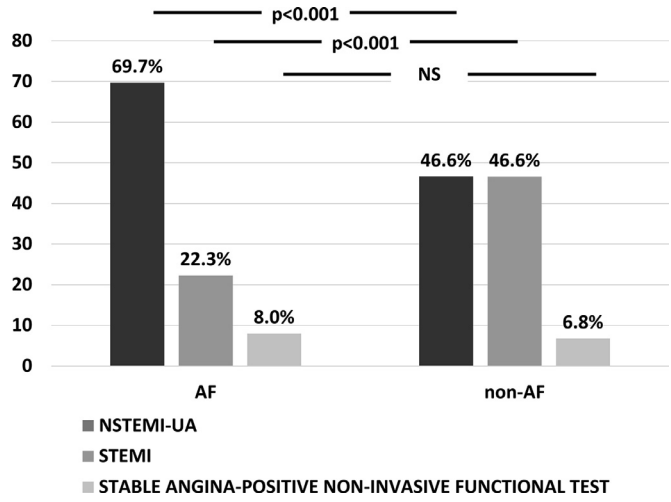

Figure 1. Proportion of NSTEMI-UA, STEMI, and stable angina in patients with and without atrial fibrillation.

lower rate of STEMI was found in the AF group (22.3% vs 46.6%, p <0.001) (Figure 1).

LAD was the most common coronary diseased vessel (70.6%) followed by RCA (56.4%) OM (36.6%) and LCX (33%) (Table 2). Patients with AF had a significantly lower RCA involvement (47.3% vs 61.8%, p = 0.016), with a trend for LAD (64.3% vs 74.3%, p = 0.069) (Table 2). Patients with LAD involvement (Table 3) were less commonly women, with a higher proportion of diabetes, previous ischemic heart disease and antiplatelet drugs use, with a nonsignificant lower prevalence of AF. Patients with LAD obstruction had also a higher 2MACE score (Table 3). On multivariable logistic regression analysis, female sex and the presence of AF were inversely associated with LAD, while previous ischemic heart disease and diabetes showing a direct association (Table 4, *Panel A*). Similar results were found using 2MACE score as covariate instead of single variables (Table 4, *Panel A*). Patients with RCA obstruction (Table 3) were less commonly affected by AF (and therefore less frequently on oral anticoagulants), with a higher prevalence of diabetes, and more commonly on Calcium channel blockers. On multivariable logistic regression analysis, AF was inversely associated with RCA involvement, while the use of Calcium channel blockers was directly associated with the risk of diseased RCA (Table 4, *Panel B*). Similar results were found using 2MACE score as covariate instead of single variables (Table 4, *Panel B*).

Overall, the mean number of diseased vessels was lower in AF than non-AF patients (p = 0.003) (Table 2). When we analysed patients with ≥3 diseased vessels, AF patients had less multivessel disease compared to non-AF (p = 0.046) (Table 2). When we analysed characteristics of patients presenting with severe CAD, as defined by a number of diseased vessels ≥3, there was a lower prevalence of women, AF and a higher proportion of elderly patients (≥75 years), hypertension, diabetes, previous ischemic heart disease (and antiplatelet drugs use) compared to patients with <3 diseased coronary vessels (Table 3). Patients with severe CAD also had a higher 2MACE score (Table 3). Among patients with AF, a similar proportion of paroxysmal AF was found between patients with and without multivessel disease (35.5% vs 49.4%, respectively, p = 0.209). On multivariable logistic regression analysis, AF was inversely associated with multivessel disease, while arterial hypertension and previous ischemic heart disease increased the risk of multivessel disease (Table 4, *Panel C*). Similar results were found using 2MACE score as covariate instead of single variables (Table 4, *Panel C*).

Table 2
Coronary involvement in patients with and without atrial fibrillation

Coronary vessel	Whole cohort (n= 303)	Atrial fibrillation		p
		No (n=191)	Yes (n=112)	
Right coronary dominance	263 (86.8)	162 (84.8%)	101 (90.2%)	0.220
Left main coronary artery	23 (7.6%)	18 (9.4%)	5 (4.5%)	0.176
Left anterior descending artery	214 (70.6%)	142 (74.3%)	72 (64.3%)	0.069
Left circumflex artery	100 (33.0%)	70 (36.6%)	30 (26.8%)	0.100
Obtuse marginal artery	111 (36.6%)	71 (37.2%)	40 (35.7%)	0.902
Right coronary artery	171 (56.4%)	118 (61.8%)	53 (47.3%)	0.016
Mean number of coronary vessels with stenosis ≥70%	2.04±1.12	2.19±1.19	1.79±1.11	0.003
Number of coronary vessels with stenosis ≥70%				0.026 (among groups)
1	112 (37.0%)	64 (33.5%)	48 (42.8%)	0.046 (for ≥3 vessels)
2	85 (28.1%)	52 (27.2%)	33 (29.5%)	
≥3	106 (34.9%)	75 (39.3%)	31(27.7%)	

Table 3
Clinical characteristics of patients with diseased LAD or RCA

	Left anterior descending artery		P	Right coronary artery.		p	≥3 vessels		p
	No (n=89)	Yes (n=214)		No (n=132)	Yes (n=171)		no (n=197)	yes (n=106)	
Age (years)	69.7±11.3	69.4±10.5	0.850	70.6±10.8	68.6±10.7	0.115	69.4±10.6	69.8±11.1	0.764
Age ≥ 75 years	32 (36.0%)	79 (36.9%)	0.897	50 (37.9%)	61 (35.7%)	0.719	65 (33.0%)	46 (43.4%)	0.081
Women	36 (40.4%)	34 (15.9%)	<0.001	35 (26.5%)	35 (20.5%)	0.220	54 (27.4%)	16 (15.1%)	0.015
Atrial fibrillation	40 (44.9%)	72 (33.6%)	0.069	59 (44.7%)	53 (31.0%)	0.016	81 (41.1%)	31 (29.2%)	0.046
Arterial hypertension	76 (85.4%)	190 (88.8%)	0.443	112 (84.8%)	154 (90.1%)	0.215	164 (83.2%)	102 (96.2%)	0.001
Diabetes	16 (18.0%)	71 (33.2%)	0.008	31 (23.5%)	56 (32.7%)	0.096	48 (24.4%)	39 (36.8%)	0.024
Chronic obstructive pulmonary disease	20 (22.5%)	43 (20.1%)	0.644	31 (23.5%)	32 (18.7%)	0.321	42 (21.3%)	21 (19.8%)	0.882
Previous ischemic heart disease	21 (23.6%)	88 (41.1%)	0.004	43 (32.6%)	66 (38.6%)	0.334	58 (29.4%)	51 (48.1%)	0.002
Heart failure	19 (21.3%)	58 (27.1%)	0.315	39 (29.5%)	38 (22.2%)	0.183	49 (24.9%)	28 (26.4%)	0.783
Previous Thromboembolism	6 (6.7%)	22 (10.3%)	0.390	15 (11.4%)	13 (7.6%)	0.318	20 (10.2%)	8 (7.5%)	0.536
CHA_2DS_2-VASc score	2.79±1.62	3.06±1.71	0.198	3.05±1.68	2.93±1.69	0.555	2.81±1.69	3.30±1.63	0.015
2MACE score	2.24±1.67	2.87±1.67	0.003	2.56±1.73	2.78±1.66	0.272	2.45±1.66	3.12±1.66	0.001
Angiotensin-converting enzyme inhibitors/ Angiotensin receptor blockers	48 (53.9%)	136 (63.6%)	0.123	77 (58.3%)	107 (62.6%)	0.478	113 (57.4%)	71 (67.0%)	0.110
Oral anticoagulants	33 (37.1%)	64 (29.9%)	0.227	53 (40.2%)	44 (25.7%)	0.009	71 (36.0%)	26 (24.5%)	0.052
Proton pump inhibitors	36 (40.4%)	98 (45.8%)	0.447	65 (49.2%)	69 (40.4%)	0.131	83 (42.1%)	51 (48.1%)	0.334
Antiplatelet drugs	25 (28.1%)	99 (46.3%)	0.005	50 (37.9%)	74 (43.3%)	0.349	71 (36.0%)	53 (50.0%)	0.020
β-Blockers	30 (33.7%)	89 (41.6%)	0.245	46 (34.8%)	73 (42.7%)	0.192	73 (37.1%)	46 (43.4%)	0.324
Calcium channel blockers	24 (27.0%)	54 (25.2%)	0.774	26 (19.7%)	52 (30.4%)	0.046	50 (25.4%)	28 (26.4%)	0.891
Statins	41 (46.1%)	115 (53.7%)	0.256	66 (50.0%)	90 (52.6%)	0.728	98 (49.7%)	58 (54.7%)	0.470

Discussion

Our study comparing angiographic characteristics of patients undergoing PCI according to the presence of AF indicates a lower involvement of RCA in AF patients, who were generally affected by a less severe obstructive CAD compared to non-AF.

We found that the most common clinical presentation of CAD in AF patients was NSTEMI-UA (69.7%), while

Table 4
Multivariable logistic regression analysis of factors associated with diseased left anterior descending artery (*Panel A*), right coronary artery (*Panel B*) or multivessel disease (≥3 vessels) (*Panel C*)

Panel A. Left anterior descending artery	Odds ratio	95% confidence interval		p
		Lower	Upper	
Female sex	0.327	0.183	0.583	<0.001
Diabetes	1.840	0.970	3.488	0.062
Atrial fibrillation	0.643	0.374	1.104	0.109
Previous ischemic heart disease	1.984	1.098	3.586	0.023
Left anterior descending artery with 2MACE score as covariate				
Female sex	0.288	0.160	0.518	<0.001
Atrial fibrillation	0.569	0.328	0.989	0.046
2MACE score	1.301	1.103	1.535	0.002
Panel B. Right coronary artery				
Atrial fibrillation	0.541	0.541	0.335	0.012
Diabetes	1.557	1.557	0.923	0.097
Calcium channel blockers	1.823	1.823	1.053	0.032
Panel C. ≥3 vessels disease				
Age ≥75 years	1.272	0.975	1.660	0.077
Female sex	0.561	0.291	1.081	0.084
Atrial fibrillation	0.470	0.272	0.810	0.007
Arterial hypertension	3.717	1.225	11.278	0.020
Diabetes	1.393	1.393	0.808	0.233
Previous ischemic heart disease	1.854	1.854	1.099	0.021
≥3 vessels with 2MACE score as covariate				
Female sex	0.477	0.477	0.249	0.026
Atrial fibrillation	0.507	0.507	0.295	0.014
2MACE score	1.330	1.330	1.140	<0.001

STEMI accounted for 22.3% of cases. These data are in keeping with a previous work showing that in 12,281 patients with paroxysmal or chronic AF, NSTEMI represented the most frequent indication to PCI (72%), followed by STEMI (27%).[9] The association between AF and NSTEMI has been previously reported in a post hoc analysis from the ARIC study which showed a nearly doubled risk of NSTEMI in AF patients compared to those without.[10] This association may have several different explanations; thus, factors precipitating partial occlusion of the coronary arteries may include reduced oxygen supply (i.e., vasospasm) or increased oxygen demand as happens during AF episodes with uncontrolled ventricular response, usually referred to as type 2 myocardial infarction without ST elevation.[11]

In our study, the LAD was the most common coronary diseased vessel (70.6%) followed by RCA (56.4%), OM (36.6%), and LCX (33%). In the randomized DEFINE-FLAIR (Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization) LAD was affected in 52%-53%, RCA in 23%-24% and LCX in 20% of patients.[12] Similarly, in the Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-SWEDEHEART) trial,[13] a diseased LAD was found in 47% to 48%, LCX in 18% to 19% and RCA in 18% to 20%. Patients included in our cohort study had more severe CAD compared to clinical trials despite a similar mean age and a similar proportion of women, as shown by the higher mean number of target vessels and the higher proportion of patients with multivessel disease, which was almost 35% in our study, as compared to iFR-SWEDEHEART trial in which only 10% of patients had 3-vessel disease.[13] Furthermore, these trials did not include patients with AF and the majority of patients undergoing PCI had stable CAD. The prevalence of 3-vessel disease was similar to a previous study including 56 AF patients, in whom 30% of patients undergoing PCI and/or coronary artery bypass grafting (CABG) had multivessel disease.[14] However, it should be considered that not only the severity of coronary stenosis or the number of diseased vessels may affect the prognosis of patients, but also the atherosclerotic burden and plaque composition. Thus, the Scottish Computed Tomography of the HEART Trial study showed that the presence of adverse plaque features, defined as positive remodeling or low attenuation plaque, and coronary artery calcification within 15 coronary segments were associated with worse outcomes.[15]

We found a less common involvement of RCA in patients with AF compared to those without (47.3% and 61.8%, respectively); this prevalence was slightly lower to that reported in a previous study which showed a diseased RCA in 62% of AF cases.[14] We also found a generally less severe CAD, as shown by the lower prevalence of multivessel coronary disease, in AF patients. This association was confirmed after adjustment for confounding factors, such as age and comorbidities. These findings might be partially explained by the early use of ACE inhibitors/ARBs and oral anticoagulants in patients once they are diagnosed with AF. Of note, oral anticoagulation with warfarin reduces the incidence of first MI infarction compared to aspirin therapy.[16] Furthermore, we might also hypothesize that patients with AF usually undergo a more structured clinical and instrumental follow-up, as indicated by guidelines both for either INR monitoring or direct oral anticoagulants control, which could allow earlier identification and management of cardiovascular risk factors (i.e., compensated diabetes and hypertension), ultimately leading to a less severe ACS presentation.

Another interesting finding of our study is the inverse association between female sex and LAD involvement, with women having a less prevalence of multivessel CAD. These data are in line with previous reports showing sex-based difference in CAD,[17] as women have been shown to have more microvascular than macrovascular obstructive disease, and to have less severe obstructive CAD compared to men.[18,19]

We also investigated in this cohort of PCI patients the value of the 2MACE score, which has been proposed as a useful tool to stratify cardiovascular risk in patients with AF.[20] We found that the 2MACE score, but not the CHA_2DS_2VASc score, was higher in patients with diseased LAD, and that it was independently associated with severe CAD, such as those with $\geq$3 vessels-disease. The potential usefulness of the 2MACE score for the identification of patients at higher risk of severe CAD requires further exploration.

This was a single-center study including elderly Caucasian only patients. Thus, the generalizability of our results to other ethnic groups is uncertain. The effect of specific drugs on the development of severe CAD cannot be explored in the present study and need to be addressed in ad hoc studies. The severity of CAD should be confirmed in AF patients treated with the direct oral anticoagulants which have been shown to reduce long-term cardiac risk compared to warfarin.[21,22] The higher proportion of AF patients seen in our study compared to previous ones may be related to the type of centers recruiting patients, as 1 of the 2 centers is specialized in the management of anticoagulation therapy in AF patients. The association between AF and RCA found in our study needs to be confirmed in larger studies. Finally, as the majority of patients presented with ACS the generalizability of our results to patients with chronic and/or stable CAD must be explored.

In conclusion, patients with AF show lower RCA involvement and generally less severe CAD compared to non-AF ones. 2MACE score was higher in LAD obstruction and identified patients with severe CAD.

Authors' Contributions

Daniele Pastori: Conceptualization; Formal analysis; Writing - original draft; Writing - review & editing. Flavio Giuseppe Biccirè: Data curation; Writing - original draft; Writing - review & editing. Gregory Yoke Hong Lip: Validation; Writing - original draft; Writing - review & editing. Danilo Menichelli: Data curation; Writing - original draft; Writing - review & editing. Pasquale Pignatelli: Validation; Writing - original draft; Writing - review & editing. Francesco Barillà: Validation; Writing - original draft; Writing - review & editing. Francesco Violi: Validation; Writing - original draft; Writing - review & editing. Carlo Gaudio:

Validation; Writing - original draft; Writing - review & editing. Gaetano Tanzilli: Supervision; Writing - original draft; Writing - review & editing.

Disclosures

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1. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 2016;354:i4482.
2. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, Herrington DM, Cushman M. Atrial fibrillation and the risk of myocardial infarction. *JAMA Int Med* 2014;174:107–114.
3. Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients. *Am J Med* 2010;123:785–789.
4. Pastori D, Pignatelli P, Saliola M, Carnevale R, Vicario T, Del Ben M, Cangemi R, Barilla F, Lip GY, Violi F. Inadequate anticoagulation by Vitamin K antagonists is associated with major adverse cardiovascular events in patients with atrial fibrillation. *Int J Cardiol* 2015;201:513–516.
5. Pokorney SD, Piccini JP, Stevens SR, Patel MR, Pieper KS, Halperin JL, Breithardt G, Singer DE, Hankey GJ, Hacke W, Becker RC, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KA, Califf RM, Committee RAS, Investigators, Investigators RASC. Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. *J Am Heart Assoc* 2016;5:e002197.
6. Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, Ivanes F, Babuty D, Lip GY. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med* 2016;129:1278–1287.
7. Pastori D, Farcomeni A, Poli D, Antonucci E, Angelico F, Del Ben M, Cangemi R, Tanzilli G, Lip GY, Pignatelli P, Violi F. Cardiovascular risk stratification in patients with non-valvular atrial fibrillation: the 2MACE score. *Intern Emerg Med* 2016;11:199–204.
8. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–224.
9. Batra G, Svennblad B, Held C, Jernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart* 2016;102:926–933.
10. Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, Loehr L, Cushman M, Alonso A. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the atherosclerosis risk in communities (ARIC) study. *Circulation* 2015;131:1843–1850.
11. Violi F, Soliman EZ, Pignatelli P, Pastori D. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. *J Am Heart Assoc* 2016;5:e003347.
12. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. *N Engl J Med* 2017;376:1824–1834.
13. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O, i FRSI. Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *N Engl J Med* 2017;376:1813–1823.
14. Kralev S, Schneider K, Lang S, Suselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PloS one* 2011;6:e24964.
15. Williams MC, Moss AJ, Dweck M, Adamson PD, Alam S, Hunter A, Shah ASV, Pawade T, Weir-McCall JR, Roditi G, van Beek EJR, Newby DE, Nicol ED. Coronary artery plaque characteristics associated with adverse outcomes in the SCOT-HEART study. *J Am Coll Cardiol* 2019;73:291–301.
16. Lee CJ, Pallisgaard JL, Olesen JB, Carlson N, Lamberts M, Gislason GH, Torp-Pedersen C, Brandes A, Husted SE, Johnsen SP, Hansen ML. Antithrombotic therapy and first myocardial infarction in patients with atrial fibrillation. *J Am Coll Cardiol* 2017;69:2901–2909.
17. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, Lindley KJ, Vaccarino V, Wang TY, Watson KE, Wenger NK, American Heart Association Cardiovascular Disease in W, Special Populations Committee of the Council on Clinical Cardiology CoE, Prevention CoC, Stroke N, Council on Quality of C, Outcomes R. Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation* 2016;133:916–947.
18. Bairey Merz CN, Shaw LJ, Reis SE, Bittner V, Kelsey SF, Olson M, Johnson BD, Pepine CJ, Mankad S, Sharaf BL, Rogers WJ, Pohost GM, Lerman A, Quyyumi AA, Sopko G, Investigators W. Insights from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006;47:S21–S29.
19. Johnston N, Schenck-Gustafsson K, Lagerqvist B. Are we using cardiovascular medications and coronary angiography appropriately in men and women with chest pain. *Eur Heart J* 2011;32:1331–1336.
20. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halvorsen S, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigli M, Huber K, Group ESCSD. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Europace* 2019;21:192–193.
21. Pastori D, Menichelli D, Del Sole F, Pignatelli P, Violi F, group A-As. Long-term risk of major adverse cardiac events in atrial fibrillation patients on direct oral anticoagulants. *Mayo Clin Proc* 2020. https://doi.org/10.1016/j.mayocp.2020.06.057.
22. Lee CJ, Gerds TA, Carlson N, Bonde AN, Gislason GH, Lamberts M, Olesen JB, Pallisgaard JL, Hansen ML, Torp-Pedersen C. Risk of myocardial infarction in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2018;72:17–26.