Risk of myocardial infarction in paroxysmal vs. non-paroxysmal atrial fibrillation: an individual patient-level data analysis of 71,466 patients from COMBINE-AF

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BACKGROUND

Prior data suggest the MI risk may be higher with paroxysmal AF (PAF) vs. non-paroxysmal AF (non-PAF). Proposed mechanisms include tachycardia-induced oxidative stress (via LOX-1) with microvascular flow abnormalities, ischemia downstream of a fixed coronary obstruction, and plaque rupture.

Our objective is to revisit this hypothesis using the larger and longer study period of the COMBINE-AF database, an individual patient-level metanalysis of the 4 pivoval RCTs of DOAC vs warfarin.

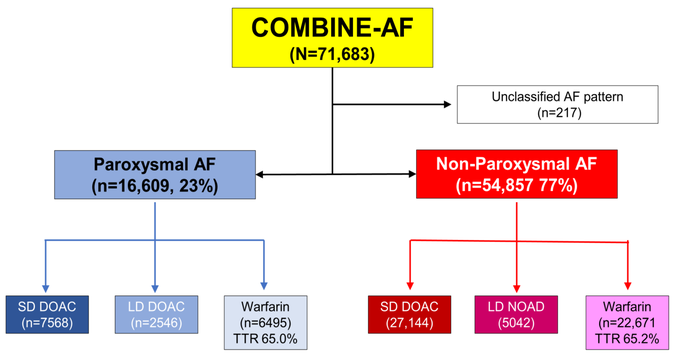
METHODS

We compared MI rates in patients with PAF vs. non-PAF in COMBINE AF, a patient-level metanalysis of 4 RCTS of DOACs vs warfarin (ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY, ROCKET AF). Secondary endpoints were ischemic stroke and CV death. Cox proportional-hazards models stratified by trial and adjusted for elements of the CHADS-VASc score were constructed. Sensitivity analyses were performed across subgroups, omitting pts on lower-dose DOAC regimens, and accounting for competing risk of death.

Prespecified outcomes were: stroke (ischemic, hemorrhagic), systemic embolic events (SEE), major bleeding (ICH, GI, other), death, and a net clinical outcome combing these events.

RESULTS

Figure 1 – Consort Diagram



DISCLOSURES

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Table 1 – Baseline Characteristics

Baseline Characteristics of Patients Stratified by the Type of Atrial Fibrillation

Variable	Overall	PAF (N=12845)	Non-PAF (N=45578)
Age			
Median (IQR)	72 (65-77)	71 (65-77)	72 (65-77)
Mean (SD)	70.4 (9.4)	70.3 (9.3)	70.5 (9.4)
<65 years	14403 (24.7%)	3141 (24.5%)	11262 (24.7%)
65 to <75 years	21643 (37%)	4904 (38.2%)	16739 (36.7%)
>=75 years	22377 (38.3%)	4800 (37.4%)	17577 (38.6%)
Female	21752 (37.2%)	5540 (43.1%)	16212 (35.6%)
Race			
White	47134 (80.7%)	10617 (82.7%)	36517 (80.1%)
Black	713 (1.2%)	152 (1.2%)	561 (1.2%)
Asian	8250 (14.1%)	1440 (11.2%)	6810 (14.9%)
Other	2325 (4%)	636 (5%)	1689 (3.7%)
Comorbidities			
Hypertension	51365 (87.9%)	11285 (87.9%)	40080 (87.9%)
Diabetes	18038 (30.9%)	3829 (29.8%)	14209 (31.2%)
Current Smoker	4212 (7.2%)	903 (7%)	3309 (7.3%)
Coronary Artery Disease	17377 (29.8%)	4234 (33%)	13143 (28.8%)
Heart Failure	27254 (46.7%)	4715 (36.7%)	22539 (49.5%)
Myocardial Infarction	8632 (14.8%)	2061 (16%)	6571 (14.4%)
Valvular Disease	10847 (18.6%)	2177 (17%)	8670 (19%)
Stroke	11099 (19%)	2276 (17.7%)	8823 (19.4%)
Transient Ischaemic Attack	7073 (12.1%)	1806 (14.1%)	5267 (11.6%)
Falls	2745 (4.8%)	849 (6.7%)	1896 (4.3%)
Creatinine Clearance (mL/min) - Median (IQR)	70 (54-90.6)	70 (54.6-90)	70 (54-90.7)
CHA2DS2VASC >=4	35194 (60.2%)	7573 (59%)	27621 (60.6%)
HAS-BLED >=3	26721 (45.7%)	6409 (49.9%)	20312 (44.6%)
Medication Use			
Aspirin	19699 (33.7%)	5202 (40.5%)	14497 (31.8%)
NSAID (other than COX II inhibitor)	2575 (4.4%)	527 (4.1%)	2048 (4.5%)
Statin	21653 (37.3%)	5462 (42.7%)	16191 (35.7%)
Randomization Group			
DOAC	29257 (50.1%)	6350 (49.4%)	22907 (50.3%)
Dose-Reduced DOAC	3671 (12.5%)	732 (11.5%)	2939 (12.8%)
Warfarin	29166 (49.9%)	6495 (50.6%)	22671 (49.7%)

All differences were statistically significant p <0.05

FIG 2 – Kaplan-Meier curves for the outcomes of myocardial infarction (left panel), ischemic stroke (middle panel) and cardiovascular death (right panel) in 16,609 patients with PAF vs. 54,857 with non-PAF

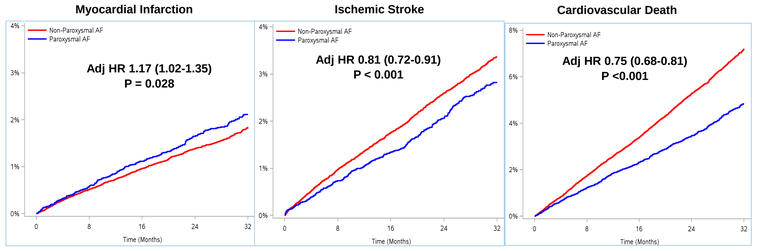


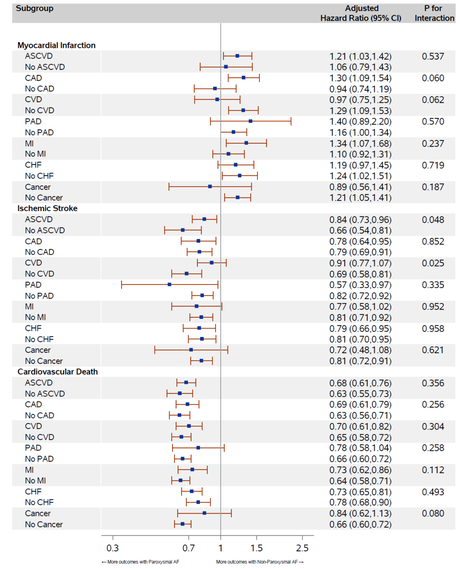
FIGURE 3 – AF Pattern and Outcome

Cox Regression Model by AF Type

	Non-PAF (N=45578)				PAF (N=12845)				
Endpoint	n	N	Event Rate % pts/yr	Hazard Ratio (95% CI)	n	N	Event Rate % pts/yr	Hazard Ratio (95% CI)	P-value
Myocardial Infarction	607	45515	0,68	Ref	203	12821	0,78	1.16 (0.99,1.36)	0,074
Ischemic Stroke	1065	45515	1,20	Ref	270	12821	1,05	0.87 (0.76,1.00)	0,047
Cardiovascular Death	2437	45515	2,72	Ref	489	12821	1,87	0.68 (0.62,0.75)	<.001
MI/Ischemic Stroke/CVD	3685	45515	4,17	Ref	860	12821	3,36	0.80 (0.74,0.86)	<.001
Non-CV Death	1469	45515	1,64	Ref	325	12821	1,25	0.78 (0.69,0.88)	<.001
HHF or HF-Related Death	2015	45515	2,30	Ref	407	12821	1,59	0.77 (0.69,0.85)	<.001
Major Bleeding	2449	45438	3,15	Ref	750	12812	3,41	1.05 (0.96,1.14)	0,297

A stratified cox proportional hazard model was used for the hazard ratios stratifying by trial

FIGURE 4 – Subgroups



DISCUSSION

Several mechanisms could explain different risks of MI in pts with PAF vs. non-PAF:

1. Direct effect of brief AF episodes on the ventricular myocardium at a cellular and microcirculatory level.
2. Higher risk for MI in patients with PAF could be due to tachycardia-induced myocardial ischemia in patients with coronary artery disease, e.g., a type 2 MI.
3. Another potential pathophysiologic mechanism could be the rupture of the coronary atherosclerotic plaque induced by tachycardia and excess circulating catecholamines.

On the contrary, in individuals with non-PAF, effective rate control together with chronic remodeling in the left atrium may counterbalance the associated flow variation and oxidative stress, rendering ventricular ischemia less likely.

LIMITATIONS

1. The main limitation of the study is that this was a post-hoc analysis of non-randomized groups, and therefore, the baseline characteristics of patients in the two groups were imbalanced. Although we adjusted our analyses for several potentially confounding variables, still unmeasured confounders may have influenced our results.
2. Another limitation is that changes in the pattern of AF might have occurred during the follow-up period. Furthermore, we could not assess the type of MI, e.g., STEMI vs. NSTEMI, Type 1 vs 2, which could provide further insight into the underlying pathophysiology.

CONCLUSION

This individual patient-level metanalysis of 71,466 patients from COMBINE AF shows that the adjusted risk of MI is higher in patients with PAF than non-PAF, while the adjusted risks of ischemic stroke and CV death were lower in patients with PAF.