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SHORT REPORT

Feasibility of anticoagulation on demand after percutaneous coronary intervention in high-bleeding risk patients with paroxysmal atrial fibrillation: the INTERMITTENT registry

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Aims This study evaluated the feasibility of the intermittent use of direct oral anticoagulants (DOACs) guided by continuous rhythm monitoring via a clinically validated wearable smart device in high-bleeding risk (HBR) patients with symptomatic paroxysmal atrial fibrillation (AF) otherwise subjected to chronic anticoagulation after percutaneous coronary intervention (PCI).

Methods and results The INTERMITTENT registry was a 3-year prospective observational study at eight Italian centres. Inclusion criteria were elective or urgent PCI, Academic Research Consortium HBR criteria, history of symptomatic 12-lead ECG detected paroxysmal AF episodes, indication to DOACs, and use of a wearable smart device (Apple Watch™). Thirty days after PCI, patients free of AF episodes discontinued DOAC. However, if an AF episode lasting >6 min or a total AF burden > 6 h over 24 h was detected, DOAC was initiated for 30 consecutive days, and withdrawn afterwards if no further AF episodes occurred. At the discretion of the referring physician, intermittent anticoagulation was offered to 89 patients, whereas continuous treatment with DOACs was prescribed to 151 patients. During a follow-up of 298 ± 87 days, the average duration of oral anticoagulation was significantly shorter in the intermittent anticoagulation group (176 ± 43 days, $P = 0.0001$), representing a 40% reduction in anticoagulation time compared to the continuous group. Ischaemic and bleeding endpoints were not significantly different between the two groups. Propensity score-matching resulted in a total of 69 matched patients with intermittent vs. continuous anticoagulation, respectively. During a follow-up of 291 ± 63 days, there was a significant 46% reduction in anticoagulation time in the intermittent compared to the continuous group ($P = 0.0001$).

Conclusion In HBR patients with a history of paroxysmal AF episodes who underwent PCI, intermittent anticoagulation guided by continuous rhythm monitoring with a wearable device was feasible and decreased significantly the duration of anticoagulation.

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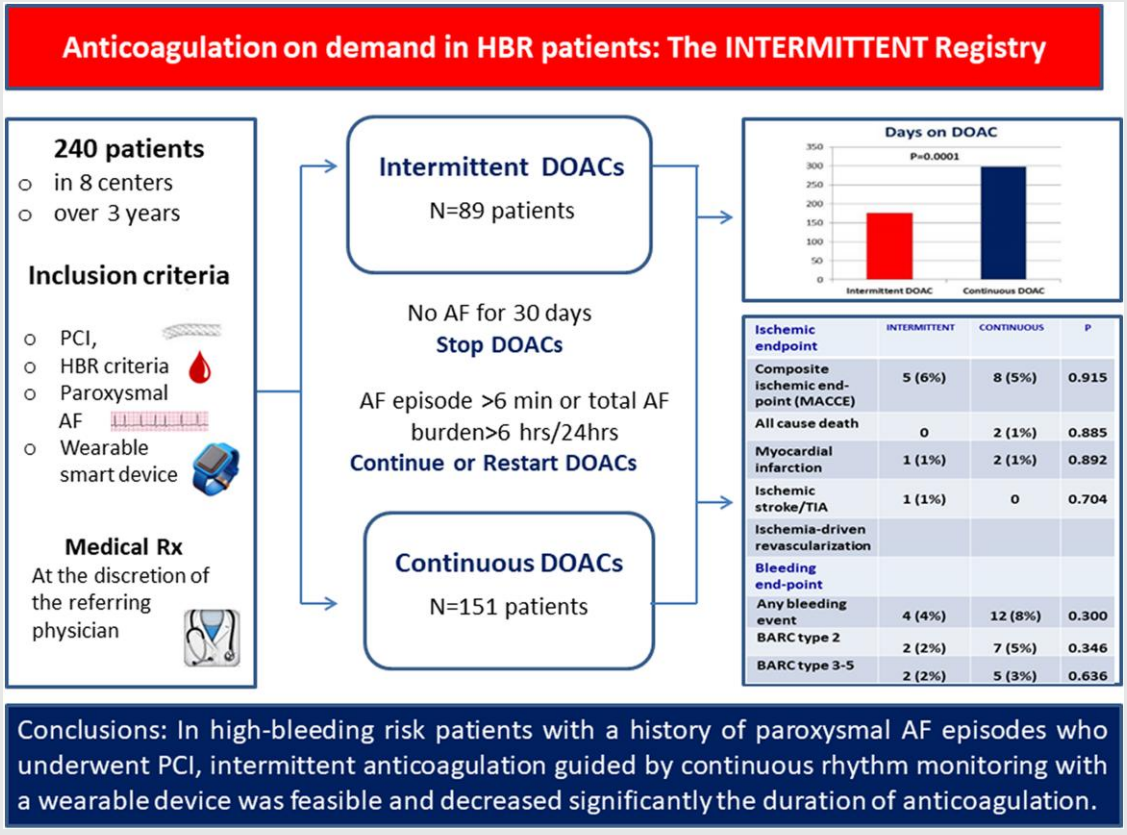
Graphical Abstract



Keywords Anticoagulation • Atrial fibrillation • Healthcare innovation • High-bleeding risk • Percutaneous coronary intervention • Wearable smart device

Direct oral anticoagulants (DOAC) are recommended in atrial fibrillation (AF) patients with thrombo-embolic risk factors.[1,2] However, chronic use of DOACs might be associated with higher risk of bleeding complications, especially in patients who are receiving antiplatelet agents after percutaneous coronary intervention (PCI).[3]

In recent years, the strategy of prescribing oral anticoagulants only when AF occurs has been tested in a few not adequately powered pilot investigations. Also known as intermittent, on demand, or 'pill in the pocket' anticoagulation, continuous rhythm monitoring guided anticoagulation with DOACs reduced bleeding risk among patients with rare AF episodes and low-to-moderate stroke risk without increasing thrombo-embolic events.[4–6] However, whether the strategy of intermittent anticoagulation is feasible also in patients undergoing PCI is unknown.

The aim of this study was to evaluate the feasibility of intermittent DOAC use guided by continuous AF monitoring via a clinically validated wearable smart device[7] in high-bleeding risk (HBR) patients with symptomatic paroxysmal AF who would otherwise receive a combination regimen of oral anticoagulation and antiplatelet agents for 6–12 months after PCI.

The INTERMITTENT registry was a 3-year prospective observational study of paroxysmal AF at eight Italian centres. Inclusion criteria were elective or urgent PCI, Academic Research Consortium HBR criteria,[8] history of symptomatic 12-lead ECG detected paroxysmal AF episodes, indication to DOAC, and use of a wearable smart device (Apple Watch™, Apple Inc., Cupertino, CA). Exclusion criteria were a prior stroke/transient ischaemic attack, persistent/permanent AF, contraindications to anticoagulation, or medical condition(s) that prohibited discontinuation of anticoagulation, current pregnancy or plans to become pregnant, or if life expectancy was <12 months. The study was carried out according to the principles of the Declaration of Helsinki, was approved by the Institutional Review Board of the University 'Sapienza' of Rome (Protocol ID: 2019/D/983), and registered at ClinicalTrials.gov (NCT04151680). All patients provided written informed consent.

All study patients underwent PCI during hospitalization and were then discharged on dual antithrombotic therapy according to current recommendations.[1,2] Treatment included a P2Y12 receptor inhibitor (i.e. clopidogrel, ticagrelor, or prasugrel) along with a DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) for 6 months in patients with chronic coronary syndrome (CCS) or 12 months after acute coronary syndrome (ACS).

During follow-up, patients were instructed to press or hold the crown of the wearable smart device for 30 s to obtain an ECG when paroxysmal AF episodes were suspected or when they received an irregular rhythm notification. At the discretion of the referring physician, a proportion of study patients were offered a strategy of intermittent anticoagulation on the basis of the TACTIC-AF criteria.[6] Specifically, patients discontinued DOAC if they were free of AF episodes lasting

Table 1 Clinical characteristics and presentation in the overall study population and pairwise-matched patients

	Overall population ($n = 240$)			Pairwise-matched patients ($n = 138$)		
	Intermittent DOAC ($n = 89$)	Continuous DOAC ($n = 151$)	*P* value	Intermittent DOAC ($n = 69$)	Continuous DOAC ($n = 69$)	*P* value
Age (years)	72 ± 10	76 ± 11	0.005	73 ± 9	73 ± 9	1.000
Female sex (%)	31 (35%)	63 (42%)	0.451	25 (36%)	25 (36%)	1.000
NYHA I–II	73 (82%)	113 (75%)	0.197	54 (79%)	55 (80%)	0.834
NYHA III–IV	16 (18%)	38 (25%)	0.198	12 (17%)	14 (20%)	0.663
Risk factors						
Family history (%)	20 (23%)	44 (29%)	0.259	14 (20%)	19 (27%)	0.318
Hypertension (%)	55 (62%)	88 (58%)	**0.024**	41 (59%)	39 (56%)	0.730
Dyslipidaemia (%)	64 (72%)	113 (75%)	0.741	48 (69%)	49 (71%)	0.852
Diabetes mellitus (%)	24 (27%)	47 (31%)	0.495	21 (30%)	19 (27%)	0.707
Smoking (%)	36 (41%)	65 (43%)	0.990	27 (39%)	28 (40%)	0.861
Past history						
Previous MI	17 (19%)	32 (21%)	0.716	12 (17%)	12 (17%)	1.000
Previous stroke	5 (6%)	15 (10%)	0.236	5 (7%)	6 (8%)	0.753
Previous PCI	19 (21%)	35 (23%)	0.722	12 (18%)	13 (19%)	0.825
Previous CABG	7 (8%)	15 (10%)	0.304	7 (10%)	6 (9%)	0.770
Co-morbidities						
Chronic kidney disease	14 (16%)	41 (27%)	**0.041**	13 (19%)	14 (20%)	0.830
PAD	23 (26%)	54 (36%)	0.116	21 (30%)	22 (32%)	0.854
COPD	5 (6%)	17 (11%)	0.143	6 (9%)	7 (10%)	0.770
Chronic liver disease	7 (8%)	20 (13%)	0.202	6 (9%)	8 (11%)	0.572
Clinical presentation						
CCS	50 (56%)	88 (58%)	0.620	40 (58%)	41 (59%)	0.862
STEMI	8 (9%)	18 (12%)	0.449	4 (6%)	5 (7%)	0.730
Unstable/NSTEMI	31 (35%)	45 (30%)	0.438	25 (36%)	23 (34%)	0.720
Ejection fraction						
LV ejection fraction < 40%	17 (19%)	33 (22%)	0.647	20 (18%)	56 (18%)	0.852
Coronary angiography						
One-vessel disease	50 (56%)	72 (48%)	0.186	38 (55%)	39 (56%)	0.863
Two- or three-vessel disease	39 (44%)	79 (52%)	0.593	31 (45%)	30 (44%)	0.864
Left main disease	1 (1%)	6 (3%)	0.205	1 (2%)	1 (2%)	1.000
Target vessel PCI						
One-vessel	59 (66%)	91 (60%)	0.351	45 (65%)	45 (66%)	1.000
Two-vessel	23 (26%)	47 (31%)	0.395	17 (24%)	18 (26%)	0.844
Three-vessel	7 (8%)	14 (9%)	0.687	6 (8%)	6 (8%)	1.000
Risk stratification						
CHADS2 score						
0	4 (5%)	5 (3%)	0.648	3 (5%)	3 (5%)	1.000
1	32 (36%)	47 (31%)	0.281	27 (39%)	25 (36%)	0.860
2	45 (51%)	83 (55%)	0.156	35 (50%)	37 (53%)	0.733
3	7 (8%)	17 (11%)	0.388	4 (6%)	4 (6%)	1.000
P2Y12 inhibitors						
Clopidogrel	58 (66%)	102 (68%)	0.849	46 (67%)	45 (65%)	0.857
Ticagrelor	21 (24%)	39 (26%)	0.869	17 (24%)	18 (26%)	0.844
Prasugrel	9 (10%)	9 (6%)	0.250	6 (9%)	6 (9%)	1.000
Antiarrhythmics						
Class I	19 (21%)	51 (34%)	**0.040**	16 (23%)	14 (21%)	0.679

Continued

Table 1 *Continued*

	Overall population ($n = 240$)			Pairwise-matched patients ($n = 138$)		
	Intermittent DOAC ($n = 89$)	Continuous DOAC ($n = 151$)	*P* value	Intermittent DOAC ($n = 69$)	Continuous DOAC ($n = 69$)	*P* value
Class III	10 (11%)	27 (18%)	0.162	7 (10%)	8 (12%)	0.784
Anticoagulant						
Dabigatran	2 (2%)	5 (3%)	0.636	1 (2%)	1 (2%)	1.000
Rivaroxaban	23 (26%)	41 (27%)	0.824	19 (27%)	19 (28%)	1.000
Apixaban	32 (36%)	57 (38%)	0.551	27 (39%)	24 (35%)	0.596
Edoxaban	32 (36%)	48 (32%)	0.886	22 (32%)	24 (35%)	0.717
Standard DOAC dose	18 (20%)	27 (18%)	0.676	16 (23%)	14 (20%)	0.564
Reduced DOAC dose	71 (80%)	124 (82%)	0.536	53 (77%)	55 (80%)	0.699
Other drugs during F/U						
Beta-blocker	71 (80%)	131 (87%)	0.152	57 (82%)	57 (83%)	1.000
ACE-I or ARB	58 (65%)	110 (73%)	0.209	42 (61%)	43 (63%)	0.861
Calcium channel blocker	10 (11%)	15 (10%)	0.762	10 (14%)	7 (10%)	0.437
Statins	81 (91%)	140 (93%)	0.636	63 (92%)	60 (87%)	0.411

ACE-I, angiotensin converting enzyme-inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BARC, Bleeding Academic Research Consortium; CABG, coronary artery by-pass grafting; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; F/U, follow-up; LV, left ventricle; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischaemic attack.

≥6 min with a total AF burden < 6 h/day at 1-month follow-up consultation. In case of DOAC discontinuation, aspirin was given in addition to the P2Y12 receptor inhibitor. Subsequently, DOAC was restarted for 30 days if an episode of transient AF lasting ≥6 min was recorded by the wearable device or AF burden surpassed the limit of total AF burden > 6 h/day.

The primary endpoint of the study was the total days on DOAC during follow-up. Secondary endpoints were adverse events, as follows: (i) an ischaemic event (i.e. acute myocardial infarction, stroke, and transient ischaemic attack); or (ii) a bleeding event (BARC types 2, 3, or 5). A 1:1 propensity score-matching was used to minimize confounding bias. Intermittently and continuously anticoagulated patients were randomly matched for age, sex, and type of clinical presentation (CCS vs. ACS).

The study population consisted of 240 patients, 146 men and 94 women. A strategy of intermittent anticoagulation was applied to 89 patients at the discretion of the referring physician, whereas continuous treatment with DOACs was prescribed to the remaining 151 patients. As compared with the intermittent group, patients who received continuous anticoagulation were significantly older, had more frequently hypertension and chronic kidney disease, and were more commonly treated with class I antiarrhythmics (*Table 1*).

During follow-up, a similar proportion of episodes of AF were recorded in the intermittent or continuous anticoagulation groups (*Table 1*). Specifically, in the intermittent anticoagulation group, no episode of AF was detected by means of the wearable device in 17 patients, whereas 1 or more episodes of AF were found in 72 patients. Of them, 45 patients had evidence of at least 1 episode per month and therefore did not withdraw anticoagulation during follow-up. In the remaining 27 patients, treatment with DOAC could be discontinued after the initial 30 days after PCI as no episodes of AF were recorded. Subsequently, these patients experienced ≥1 episode(s) of AF (mean: 1.3 ± 0.3 episodes) and therefore restarted DOAC treatment for 30 days. Of note, all AF episodes detected by the wearable smart device were confirmed in the 12 patients who also had an implantable device. During a follow-up of 298 ± 87 days, the average duration of oral anticoagulation was significantly shorter in the intermittent anticoagulation group (176 ± 43 days, $P = 0.0001$), representing a 40% reduction in anticoagulation time compared to the continuous group. Ischaemic endpoints and BARC 2–5 bleeding events were not different between the intermittent and continuous anticoagulation groups (*Table 2*).

Propensity score-matching resulted in a total of 69 matched patients with intermittent vs. continuous anticoagulation, respectively. There were no significant differences in any baseline clinical characteristics between the matched patient groups (*Table 1*). During a follow-up of 291 ± 63 days, the average duration of oral anticoagulation was significantly shorter in the intermittent anticoagulation group (156 ± 47 days, $P = 0.0001$), representing a 46% reduction in anticoagulation time compared to the continuous group (*Table 2*).

The results of our registry confirm previous findings and extend them to the post-PCI setting.[4–6] Two single-arm pilot studies have demonstrated the feasibility of this approach. REACT.COM (Rhythm Evaluation for Anticoagulation With Continuous Monitoring)[5] and TACTIC-AF (Tailored Anticoagulation for Non-Continuous Atrial Fibrillation)[6] used continuous remote monitoring from insertable cardiac monitors and dual chamber pacemakers or defibrillators, respectively, to reinitiate anticoagulation for 30 days after an AF episode of pre-specified duration. In REACT.COM, a 94% reduction in anticoagulation use was observed using a 1 h-duration threshold for anticoagulation reinitiation.[5] TACTIC-AF observed a 75% reduction in time on anticoagulation using a threshold of 6 min or total burden > 6 h/day.[6] Similarly to these previous findings, our results are in keeping with the concept that current wearable technology has the potential to be a non-invasive, inexpensive, patient-facing AF monitoring system that might allow physicians to tailor anticoagulation in multiple conditions,[9] including the post-PCI phase.

Our study has limitations. It included only a relatively small number of patients and was not powered to assess for adverse events and other safety outcomes. Indeed, the study was primarily designed to show feasibility of intermittent anticoagulation in the post-PCI setting. Although no significant adverse thrombo-embolic events were observed, our findings do not suggest that intermittent anticoagulation

Table 2 Outcome in the overall study population and pairwise-matched patients

	Overall population ($n = 240$)			Pairwise-matched patients ($n = 138$)		
	Intermittent DOAC ($n = 89$)	Continuous DOAC ($n = 151$)	*P* value	Intermittent DOAC ($n = 69$)	Continuous DOAC ($n = 69$)	*P* value
Follow-up						
Days of F/U	289 ± 66	298 ± 87	0.401	285 ± 59	291 ± 63	0.564
Patients with no AF episode during follow-up	17 (19%)	33 (22%)	0.945	14 (20%)	18 (26%)	0.905
Patients with <1 AF episode/month	27 (30%)	42 (28%)	0.922	20 (29%)	17 (25%)	0.806
Patients with ≥1 AF episode/month	45 (51%)	76 (50%)	0.804	35 (51%)	34 (49%)	0.844
Days on DOAC	176 ± 43	298 ± 87	0.0001	156 ± 47	291 ± 63	0.0001
Ischaemic endpoint						
Composite ischaemic endpoint (MACCE)	5 (6%)	8 (5%)	0.915	4 (5%)	4 (5%)	1.000
All cause death	0	2 (1%)	0.885	0	1 (1%)	0.999
Myocardial infarction	1 (1%)	2 (1%)	0.892	1 (1%)	1 (1%)	1.000
Ischaemic stroke/TIA	1 (1%)	0	0.704	1 (1%)	0	0.999
Ischaemia-driven revascularization	3 (3%)	4 (3%)	0.748	2 (3%)	2 (3%)	1.000
Bleeding endpoint						
Any bleeding event (BARC 2–5)	4 (4%)	12 (8%)	0.300	3 (4%)	5 (7%)	0.466
BARC type 2	2 (2%)	7 (5%)	0.346	2 (3%)	3 (4%)	0.648
BARC types 3–5	2 (2%)	5 (3%)	0.636	1 (1%)	2 (3%)	0.559

ACE-I, angiotensin converting enzyme-inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; BARC, Bleeding Academic Research Consortium; CABG, coronary artery by-pass grafting; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; F/U, follow-up; LV, left ventricle; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; TIA, transient ischaemic attack.

is equivalent to continuous anticoagulation, which remains the current standard of care. The use of aspirin in those who discontinued DOAC could have increased the risk of bleeding in the intermittent group. The fact that only patients with a wearable device were included in the present study may constitute a potential selection bias and should be considered when interpreting the results. Another potential limitation of our study is the fact that there were no criteria for assigning patients to the intermittent or continuous anticoagulation groups other than the physicians' discretion. Also, one should consider that uncertainty exists over the minimum duration of AF associated with stroke, which varied from minutes to hours in previous work.[10] Finally, the possibility exists that the true AF burden was underestimated by the wearable device, therefore causing undertreatment of patients who were offered intermittent anticoagulation.

In conclusion, in HBR patients with a history of paroxysmal AF episodes who underwent PCI, intermittent anticoagulation guided by continuous rhythm monitoring with a wearable device was feasible and decreased significantly the duration of anticoagulation. Although the strategy of withdrawing aspirin rather than DOAC is the currently recommended option in patients with AF undergoing PCI, our current study supports the notion that withdrawing DOAC could constitute an alternative option for AF patients undergoing PCI. In the future, direct head-to-head comparative studies with withdrawing either aspirin or DOAC are required to test and validate the specific therapeutic value of both strategies on study outcome.

Notes

Participating centres

Francesco Pelliccia (Rome, Italy), Giuseppe Marazzi (Rome, Italy), Luca Cacciotti (Rome, Italy), Alessio Arrivi (Terni, Italy), Amir Kol (Rieti, Italy), Attilio Placanica (Tivoli, Italy), Nino Cocco (Rome, Italy), Marco Zimarino (Chieti, Italy).

Conflict of interest: none declared.

Data availability

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

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