JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 79, NO. 5, 2022

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Patients With Atrial Fibrillation and PCI or ACS

Does Predicted Risk Matter?*

Pascal Vranckx, MD, PhD,[a,b] Dominick J. Angiolillo, MD, PhD,[c] Marco Valgimigli, MD, PhD[d]

Approximately, 1 in 5 patients with atrial fibrillation (AF) will undergo percutaneous coronary intervention (PCI) or experience an acute coronary syndrome (ACS). In light of their concomitant need for long-term oral anticoagulation therapy (OAC), these patients face the challenge of identifying the optimal antithrombotic strategy to prevent thrombotic recurrences.[1] In fact, the combination of an OAC with dual antiplatelet therapy (DAPT), also known as triple antithrombotic therapy, is associated with a >3-fold increase in the risk of major bleeding.[2,3] Therefore, defining antithrombotic regimens that can reduce bleeding risk without increasing the incidence of coronary or cardioembolic events has been a topic of extensive investigations.[4-7] Results of randomized clinical trials support the preferential use of a direct oral anticoagulant over a vitamin K antagonist (VKA) in patients with AF who undergo PCI or experience an ACS.[4-7] However, the most safe and effective DAPT regimen remains uncertain. Recommendations from both Europe and North America are now more aligned and recommend that the default duration of DAPT therapy should be limited to the peri-PCI period (ie, up to 1-week post-PCI), after which aspirin should be discontinued.[8,9] Moreover, clopidogrel should be the $P2Y_{12}$ inhibitor of choice. However, guideline and consensus recommendations also allow for variations in such regimen, in terms of DAPT duration and choice, which should be guided by a balanced assessment of competing risks: thrombosis (stent and non-stent related) and bleeding.[8,9] This assessment might include demographic and clinical variables, as well as PCI complexity and procedural success. Ideally, it would be desirable for practitioners to personalize the duration of DAPT based on a prediction rule that easily identifies patients at high bleeding risk and separates patients who may potentially benefit from shortening DAPT (eg, high bleeding and low ischemic risks) vs prolonging DAPT (eg, high bleeding risk and high ischemic risk).

SEE PAGE 417

In this issue of the *Journal*, Harskamp et al[10] shed some light on this matter by exploring in a substudy of the AUGUSTUS (Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs VKA and Aspirin vs Aspirin-Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) trial, the safety and efficacy of the 4 tested antithrombotic regimens according different bleeding and cerebrovascular ischemic risk, defined using the HAS-BLED[11] and CHA_2DS_2-VASC scores,[12] respectively. The authors report no statistical heterogeneity of response across the different risk categories and conclude that a treatment regimen of apixaban and a $P2Y_{12}$ inhibitor, mostly clopidogrel, with aspirin limited to the peri-PCI phase is preferable across a wide range of bleeding and stroke risk

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium; [b]Faculty of Medicine and Life Sciences, Hasselt University, Hasselt, Belgium; [c]Division of Cardiology, University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, USA; and the [d]Cardiocentro Institute, Ente Ospedaliero Cantonale, Università della Svizzera Italiana (USI), Lugano, Switzerland.

Athena Poppas, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2021.11.034

patients with AF in the first 6 months following an ACS or PCI. It may be argued that the findings from this post hoc analysis cannot be conclusive in light of a number of considerations, as outlined in the following text.

Neither the CHA_2DS_2-VASC nor the HAS-BLED scores were developed to guide an antithrombotic regimen in patients with AF who underwent PCI or experienced an ACS. Hence, the consistency of findings on outcomes in the different subgroups are not of surprise. The use of other scores could have potentially allowed to unravel some differences, as suggested in a similar analysis of the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention).[13] In contrast to HAS-BLED, the PRESISE-DAPT score,[14] at a standard bleeding risk cut-off ≥25, proved to be well calibrated for International Society of Thrombosis and Haemostasis[15] major and clinical relevant nonmajor bleeds. Thus, the PRECISE-DAPT score, although developed for the prediction of out-of-hospital bleeding among DAPT-treated patients, might be considered to identify the antithrombotic regimen intensity with the best benefit-risk ratio in an individual patient with AF having PCI also treated with an OAC.[13,16,17] It should be acknowledged that both studies were secondary analysis of a trials testing outcomes in patients with AF and undergoing PCI, a clinical scenario where capturing the risk of thrombotic and bleeding events is even more complex than in the general PCI population.[5,6] Individual components that identified an increased risk of bleeding (eg, age, prior bleeding history, renal function, stroke risk) were largely identical in the AUGUSTUS and RE-DUAL trial analysis.[13] Yet, 2 different risk scores that weighed these similar covariates differently lead to different conclusions,[13] which highlights that more work has to be done to better profile and predicting bleeding risk among OAC patients.

Defining the optimal duration of DAPT in the aforementioned analysis may be hampered by the fact that risk factors for bleeding and thrombotic complications overlap.[18] When both ischemic and bleeding risk factors are present, the risk factors for bleeding emerged as most impactful on decision making regarding DAPT duration among patients without an indication for OAC.[19] In patients with AF undergoing PCI, OAC treatment by itself may already be considered a major bleeding risk.[20] In this scenario, as acknowledged in the 2021 North American consensus document, the Academic Research Consortium High Bleeding Risk consensus criteria may be valuable to further stratify and individualize bleeding risks.[8,16,17] In validation studies with incremental risk criteria, beyond OAC use, a further increase in bleeding risk is noted.[8,21,22]

Categorizing a patient as having high bleeding risk is challenged by the notion that the risk for bleeding is dynamic by nature and might change over time, a process that cannot necessarily be accounted for when limited to in-hospital criteria. As such, risk scores based on baseline variables, even when useful to improve the accuracy of the prognostic assumptions affecting clinical decisions, cannot be considered a clear-cut decision rule or a substitute for case-by-case critical judgment (**Table 1**). The key question remains in which patient should aspirin be prolonged beyond the peri-PCI phase (ie, up to 1 week) to mitigate coronary (stent and nonstent-related) more than cerebrovascular events. In AUGUSTUS, 30 days of triple therapy appears, in the authors' words, to be the *tipping point*, with continued use of aspirin thereafter resulting in increased bleeding without significantly reducing ischemic events, which is in line with the recent results of the MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated Versus Standard DAPT Regimen) trial.[16,17]

In the era of precision medicine, particularly in the setting of complex patients such as those with an indication for OAC due to AF, and with recent PCI and/or ACS, personalizing antithrombotic treatment regimens based on calibrated risk scores is an unmet need and warrants future investigation.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Vranckx has received personal fees from Daiichi-Sankyo, Bayer AG, CSL Behring, and AstraZeneca. Dr Angiolillo has received consulting fees or honoraria from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; has received payments for participation in review activities from CeloNova and St Jude Medical; and his institution has received research grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co, Merck, Novartis, Osprey Medical, Renal Guard Solutions, and the Scott R. MacKenzie Foundation. Dr

TABLE 1 OAC Medium to Long-Term and PRECISE DAPT: Score Characteristics

	ABC[23]	ATRIA[24]	HAS-BLED[10]	HEMORRHAGES[25]
Year of publication	2016	2011	2010	2006
Patients, n	14,537 (ARISTOTLE)	6,123	3,978	3,791
Patient population	AF on OAC or NOAC	Nonvalvular AF on warfarin	Nonvalvular AF	AF
Bleeding outcome	Major bleeding at median 1.7 y	Major bleeding at median 3.5 y	Major bleeding at 1 y	Bleeding requiring hospitalization at follow-up
Bleeding definition	ISTH adapted	Protocol definition	Protocol definition	Bleeding requiring hospitalization
Score range	0 to 45	0 to 10	0 to 9	0 to 12
Development discrimination	AUC = 0.68	AUC = 0.74	AUC = 0.72	AUC = 0.67 (W treated)
Validation discrimination	AUC = 0.71	AUC = 0.74	None	None
Validating dataset	n = 8,468	n = 3,063 (derivation: validation 2:1)	None	None
Validating dataset	RE-LY	0 to 10	None	None

Scores: ABC (Age, biomarkers, clinical history)[23]; ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation[24]; HAS-BLED[10]; HEMORRHAGES[25]; Kuijer et al[26]; OBRI (Outpatient Bleeding Risk Index)[27]; ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation)[28]; PRECISE-DAPT (The Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy Score)[14]; RIETE (Receiving Anticoagulant Therapy for *Venous Thromboembolism*)[29]; Shireman et al.[30]

AF = atrial fibrillation; AUC = area under the curve; DVT = deep vein thrombosis; GI = gastrointestinal; ISTH = International Society on Thrombosis and Hemostasis; PCI = percutaneous coronary intervention; PE = pulmonary embolism; TIMI = Thrombolysis In Myocardial Infarction; VTE = venous thromboembolism.

Continued on the next page

Valgimigli has received grants and personal fees from Terumo; and has received personal fees from AstraZeneca, Alvimedica/CID, Abbott Vascular, Daiichi-Sankyo, Bayer, CoreFlow, Idorsia Pharmaceuticals LTD, Universität Basel, Dept Klinische Forschung, Vifor, Bristol Myers Squibb SA, Biotronik, Boston Scientific, Medtronic, Vesalio, Novartis, Chiesi, and PhaseBio.

ADDRESS FOR CORRESPONDENCE: Dr Pascal Vranckx, Hartcentrum Hasselt, Jessa ziekenhuis, Stadsomvaart 11, 3500 Hasselt, Belgium. E-mail: Pascal.Vranckx@jessazh.be. Twitter: @pascal_vranckx.

REFERENCES

1. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74:83–99.

2. van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. *Circulation*. 2019;139:775–786.

3. Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170:1433–1441.

4. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–2434.

5. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–1524.

6. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. *N Engl J Med*. 2019;380:1509–1524.

7. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394:1335–1343.

8. Angiolillo DJ, Bhatt DL, Cannon CP, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation*. 2021;143:583–596.

9. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the Diagnosis and Management of Atrial Fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498.

10. Harskamp RE, Fanaroff AC, Lopes RD, et al. Antithrombotic therapy in patients with atrial fibrillation after acute coronary syndromes or percutaneous intervention. *J Am Coll Cardiol*. 2022;79(5):417–427.

11. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093–1100.

12. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.

13. Costa F, Valgimigli M, Steg PG, et al. Antithrombotic therapy according to baseline bleeding risk in patients with atrial fibrillation undergoing percutaneous coronary intervention: applying the PRECISE-DAPT score in RE-DUAL PCI. *Eur Heart J Cardiovasc Pharmacother*. Published online Dec 1, 2020. https://doi.org/10.1093/ehjcvp/pvaa135

TABLE 1 Continued

Kuijer et al[26]	OBRI[27]	ORBIT-AF[28]	PRECISE-DAPT[14]	RIETE[29]	Shireman et al[30]
1999	1998	2015	2017	2008	2006
241	556	7,411	14,963	13,047	19,875
VTE (DVT or PE)	Warfarin patients (VTE, cardiac surgery, AF)	AF on OAC	Stable and unstable undergoing PCI	VTE (DVT or PE)	>65 y AF on warfarin
Bleeding during 3 mo anticoagulation	Major bleeding up to 48 mo	Major bleeding at median 2 y	Major or minor bleeding out-of-hospital (≥7 d after PCI), median follow-up 552 d	Major bleeding within 3 mo	GI or Intracranial bleeding within 3 m
Protocol definition	Protocol definition	ISTH criteria	TIMI bleeding definition	Protocol definition	Hospitalization for GI or intracranial
0 to 5.1	0 to 4	0 to 7	0 to 100	0 to 8	Dedicated formula
AUC = 0.75 (all bleeding) and 0.82 (major bleeding)	AUC = 0.72	AUC = 0.67	AUC = 0.73	None	None
None	AUC = 0.78	AUC = 0.62	AUC = 0.70 and 0.66	None	AUC = 0.63
n = 780	n = 264	n = 14,264	n = 8,595 and n = 6,172	n = 6,572	n = 6,470
Columbus Investigator study	Cleveland Univ Hospitals (1986-1987)	ROCKET-AF	PLATO and Bern-PCI Registry	RIETE	National Registry AF

14. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389:1025–1034.

15. Schulman S, Angerås U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204.

16. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385:1643–1655.

17. Smits PC, Frigoli E, Tijssen J, et al. Abbreviated antiplatelet therapy in patients at high bleeding risk with or without oral anticoagulant therapy after coronary stenting: an open-label, randomized, controlled trial. *Circulation*. 2021;144:1196–1211.

18. Capodanno D, Angiolillo DJ. Tailoring duration of DAPT with risk scores. *Lancet*. 2017;389:987–989.

19. Costa F, Van Klaveren D, Feres F, et al. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. *J Am Coll Cardiol*. 2019;73:741–754.

20. Urban P, Mehran R, Colleran R, et al. Defining high bleeding risk in patients undergoing percutaneous coronary intervention. *Circulation*. 2019;140:240–261.

21. Ueki Y, Bär S, Losdat S, et al. Validation of the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria in patients undergoing percutaneous coronary intervention and comparison with contemporary bleeding risk scores. *EuroIntervention*. 2020;16:371–379.

22. Cao D, Mehran R, Dangas G, et al. Validation of the Academic Research Consortium high bleeding risk definition in contemporary PCI patients. *J Am Coll Cardiol*. 2020;75:2711–2722.

23. Hijazi Z, Oldgren J, Lindbäck J, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet*. 2016;387:2302–2311.

24. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58:395–401.

25. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713–719.

26. Kuijer PM, Hutten BA, Prins MH, Büller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. *Arch Intern Med*. 1999;159:457–460.

27. Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med*. 1998;105:91–99.

28. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J*. 2015;36:3258–3264.

29. Ruíz-Giménez N, Suárez C, González R, et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost*. 2008;100:26–31.

30. Shireman TI, Mahnken JD, Howard PA, Kresowik TF, Hou Q, Ellerbeck EF. Development of a contemporary bleeding risk model for elderly warfarin recipients. *Chest*. 2006;130:1390–1396.

KEY WORDS antithrombotic therapy, apixaban, atrial fibrillation, bleeding, risk scores, stroke