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EDITORIAL COMMENT

Evidence and Recommendations for Uninterrupted Versus Interrupted Oral Anticoagulation in Patients Undergoing Percutaneous Coronary Intervention*

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An increasing proportion of patients on long-term oral anticoagulation (OAC), including vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), undergo invasive coronary evaluation with the intent to perform percutaneous coronary intervention (PCI), which poses a dilemma for how to manage their antithrombotic therapy (1). In particular, clinicians are faced with the decision of whether to perform the coronary transcatheter procedure on "interrupted OAC" (i.e., after interrupting OAC and allowing a washout of its effects) versus "uninterrupted OAC" (i.e., without interruption of OAC). This decision applies to patients requiring nonemergent invasive procedures such as those performed electively for chronic coronary syndromes or urgently (prior to discharge) for non-ST-segment elevation acute coronary syndrome (NSTE-ACS), in whom the invasive management can be deferred for a duration that allows the effects of OAC to wane. Although the "interrupted OAC" approach is commonly chosen to reduce the theoretical risk for peri-procedural bleeding, comparative outcomes between "interrupted OAC" and "uninterrupted OAC" are limited (2). These considerations support the need for studies specifically aimed at addressing the safety and efficacy of these 2 pre-procedural management strategies.

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In this issue of *JACC: Cardiovascular Interventions*, Venetsanos et al. (3) report the results of a retrospective analysis from the SWEDEHEART (The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry exploring efficacy and safety outcomes of uninterrupted versus interrupted OAC among patients (n = 6,485, 80% with NSTE-ACS) who were admitted while on long-term OAC and underwent nonemergent coronary angiography followed by PCI (88.4%) or by an intracoronary diagnostic procedure (11.6%) for functional or imaging assessment (3). Patients in the uninterrupted OAC group (n = 3,163) had similar rates of major adverse cardiac and cerebrovascular events (MACCE) (including death, myocardial infarction, or stroke) at 120 days (8.2% vs. 8.2%) as well as in-hospital major bleeding (2.3% vs. 2.5%) or major or minor bleeding (4.0% vs. 4.1%) compared with the interrupted OAC group. The lack of significant differences in MACCE and in-hospital bleeding was confirmed after extensive adjustment for the several baseline differences and confounders by means of 3 statistical methods, including a multivariate model and 2 propensity score-based analyses, namely the inverse probability of treatment weighting and the matched comparison involving 2,108 subjects in each treatment group. Also, no significant

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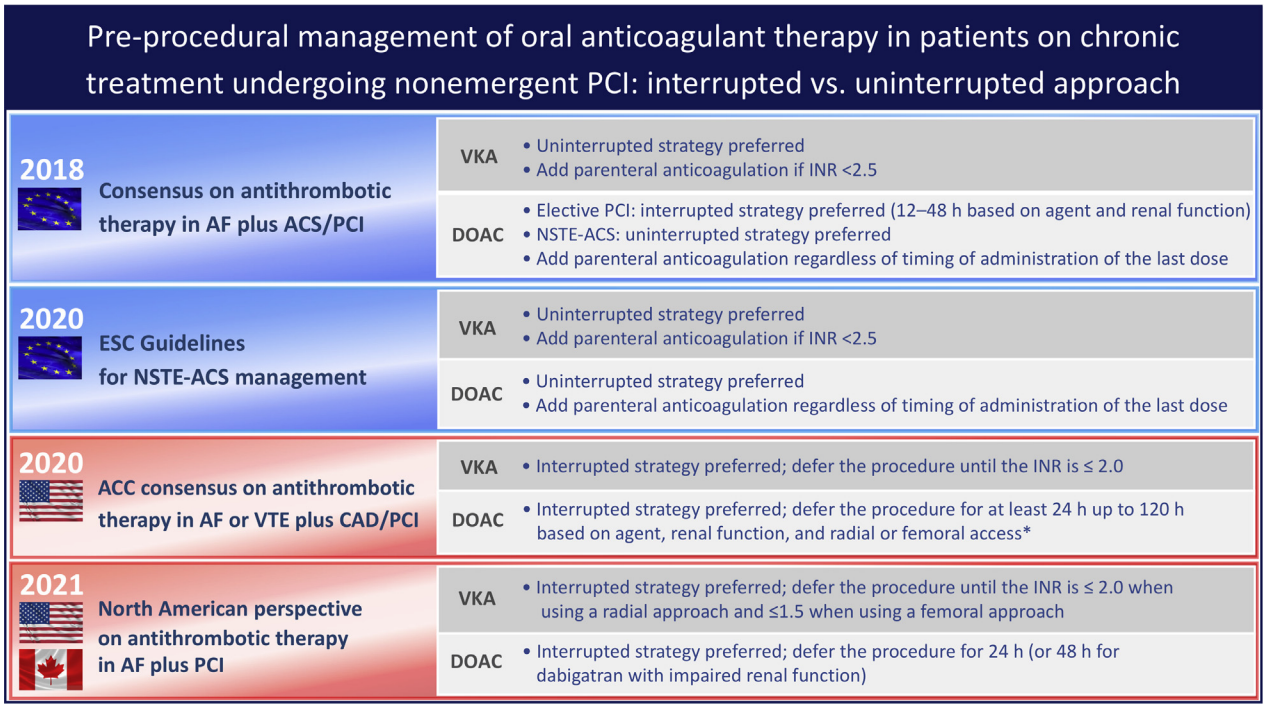
FIGURE 1 **Guidelines and Expert Consensus Recommendations on the Management of Oral Anticoagulation Before Performing a Nonemergent Coronary Invasive Procedure**



*The following recommendations for holding a direct oral anticoagulant (DOAC) before transradial percutaneous coronary intervention (PCI) are provided: apixaban, edoxaban, and rivaroxaban should be discontinued for ≥24 h if creatinine clearance is ≥30 ml/min or ≥36 h if creatinine clearance is 15 to 29 ml/min; duration of these 3 anticoagulants should be guided by agent-specific anti-Xa level or discontinuation should be ≥48 h if creatinine clearance is <15 ml/min; dabigatran should be discontinued for ≥24 h if creatinine clearance is ≥80 ml/min, ≥36 h if creatinine clearance is ≥50 to 79 ml/min, ≥48 h if creatinine clearance is ≥30 to 49 ml/min, or ≥72 h if creatinine clearance ≥15 to 29 ml/min; duration of dabigatran should be guided by diluted thrombin time or discontinuation should be ≥96 h if creatinine clearance is <15 ml/min. The following recommendations for holding a DOAC before transfemoral PCI are provided: apixaban, edoxaban, and rivaroxaban should be discontinued for ≥48 h if creatinine clearance is ≥30 ml/min; duration of these 3 anticoagulants should be guided by agent-specific anti-Xa level or discontinuation should be ≥72 h if creatinine clearance is <29 ml/min; dabigatran should be discontinued for ≥48 h if creatinine clearance is ≥80 ml/min, ≥72 h if creatinine clearance is ≥50 to 79 ml/min, ≥96 h if creatinine clearance is ≥30 to 49 ml/min, or ≥120 h if creatinine clearance is ≥15 to 29 ml/min; duration of dabigatran should be guided by diluted thrombin time if creatinine clearance is <15 ml/min. ACC = American College of Cardiology; ACS = acute coronary syndrome(s); AF = atrial fibrillation; CAD = coronary artery disease; DOAC = direct oral anticoagulant; ESC = European Society of Cardiology; INR = international normalized ratio; NSTE-ACS = non-ST-segment elevation acute coronary syndrome(s); PCI = percutaneous coronary intervention; VKA = vitamin K antagonist; VTE = venous thromboembolism.

differences in the adjusted risk for the individual components of MACCE were observed. Of note, no significant interaction was found between the type of OAC (VKA vs. DOAC) and the comparative efficacy and safety outcomes. Finally, the uninterrupted versus interrupted OAC strategy was associated with a significantly shorter median duration of hospital stay (4 days [interquartile range: 3 to 7 days] vs. 5 days [interquartile range: 3 to 8 days]).

The investigators should be commended for conducting this analysis from an all-comers national registry (from 2005 to 2017), which is to date the largest to investigate the efficacy and safety of uninterrupted compared with interrupted OAC before unplanned PCI. Moreover, this is the first study to include patients treated with DOACs (n = 1,000), although used in the minority of the study population (15%), which is reflective of the uptake of these agents not until 2013. Thus, although this study was not randomized and the potential for residual confounders cannot be excluded even after adjustments, it provides the best available data assessing differences between uninterrupted and interrupted OAC in unplanned PCI. Consistent findings have also been shown in previous studies represented by small observational or trial subgroup analysis, which mostly included VKA-treated patients undergoing planned PCI (2). Thus, the results of the

SWEDEHEART analysis contribute to reducing the gap in evidence on pre-procedural management of OAC in patients undergoing PCI.

Despite the importance of the data derived from this analysis of SWEDEHEART, a number of limitations are worthy of mentioning. First, the level of anticoagulation in terms of international normalized ratio (INR) values in patients treated with VKAs at the time of intervention was not reported. Thus, it remains unknown if a small difference in INR between the 2 groups could have blunted any difference in outcomes. In contrast, the presence of high INR values also cannot be excluded in the uninterrupted OAC group. However, it is unlikely that the invasive procedure would have been performed in the presence of a high INR. Indeed, although an INR cutoff value above which bleeding increases among patients undergoing PCI has not been identified, it is reasonable to avoid, if possible, to perform a procedure in patients with values higher than the upper therapeutic range (e.g., INR >3) when adopting an uninterrupted OAC strategy.

Second, the timing of intervention from the last dose of DOAC was not reported. Therefore, it remains unknown whether different times of intake of the last DOAC dose in this study could have affected the safety outcomes. Indeed, it is plausible that a greater time lapse between the intervention and peak plasma concentrations (about 3 h after dug intake) may be associated with enhanced safety.

Third, it remains unclear how the SWEDEHEART results apply to patients treated with femoral access, known to be at increased risk for bleeding compared with radial access. Femoral access was still performed in a relevant proportion of patients (34.6%), but whether there was an interaction between the effect of uninterrupted versus interrupted OAC and access site remains unclear from this report. Currently, radial access is the default approach, as it has been shown to reduce bleeding compared with femoral access, including among patients undergoing PCI on uninterrupted OAC (4). However, the need to use the femoral artery for access after failure of radial access is not infrequent (5), and the decision to proceed with the procedure on uninterrupted OAC should be made on a case-by-case basis.

Fourth, details of adjunctive parenteral anticoagulation therapy used during PCI are not reported, thus limiting the replicability of the overall uninterrupted OAC strategy in clinical practice.

Fifth, it remains unclear if the observed reduction in length of hospital stay with uninterrupted versus interrupted OAC may apply to present-day practice, in which DOACs, characterized by faster onset and offset of action compared with VKAs, are more commonly used.

Pre-procedural management of OAC in patients on long-term treatment has been subject of controversies, as also reflected in practice guidelines and consensus recommendations (**Figure 1**). Recommendations from Europe support the use of an uninterrupted OAC strategy for nonemergent PCI in patients with NSTE-ACS and in VKA-treated patients needing elective PCI (6,7). On the contrary, recommendations from North America indicate that performing invasive procedures using an uninterrupted OAC approach should be reserved only for very urgent or emergency procedures, while an interrupted OAC strategy should be used for all nonemergent PCI. In particular, in VKA-treated patients, nonemergent PCI should be deferred until the INR is ≤2 for radial access and ≤1.5 for femoral access; for patients on DOACs, interruption of therapy for 24 h (or 48 h for patients on dabigatran with impaired renal function) is sufficient in most cases (8,9). After discontinuation of OAC, patients with acute coronary syndromes with planned invasive management should receive parenteral anticoagulation according to usual practice, while this is not required for patients with stable coronary artery disease (8,9). After PCI, when VKAs are restarted, patients at high risk for stroke may be considered for bridging with parenteral anticoagulation until the INR is in the therapeutic range; for patients on DOACs, bridging is not required (8,9). Although the results of the SWEDEHEART registry support the European recommendations, randomized evidence is ideally needed to implement the uninterrupted OAC strategy routinely in clinical practice. Moreover, adoption of the uninterrupted OAC strategy in patients undergoing PCI is further challenged by the uncertainty surrounding the optimal antithrombotic regimen to be used during the PCI procedure. European recommendations suggest that during PCI, additional parenteral anticoagulation is recommended, irrespective of the timing of the last dose of all DOACs and if INR is <2.5 in VKA-treated patients (6,7). The need for adjunctive parenteral anticoagulation in patients on DOACs is based on data showing that DOACs may not provide sufficient anticoagulation during PCI (10). In contrast, in patients on VKAs with INRs ≥2.5, it has been suggested to either not administer additional intraprocedural anticoagulation or consider a lower heparin dose regimen (7). However, there are no data to support the safety and efficacy of these recommendations.

In conclusion, the results of the SWEDEHEART registry showed similar safety and efficacy outcomes

associated with uninterrupted and interrupted OAC strategies among patients undergoing PCI, suggesting that either of these approaches can be an option in clinical practice. Multiple factors, including the bleeding and thrombotic risk profiles of the individual patient, clinical indication of the procedure, or logistical needs may influence the decision to choose one strategy over the other. For instance, the uninterrupted OAC approach may be considered in patients at high thrombotic risk, especially those treated with VKAs, or in the setting of nonemergent PCI for NSTE-ACS, in which the time required for interrupted OAC would significantly delay the invasive treatment and affect length of stay. The use of a DOAC overcomes many of these challenges. However, if uninterrupted OAC is still considered, patients should not be at high bleeding risk or have increased probability of radial access failure or high risk for vascular complications. Thus, in appropriately selected conditions, and with the adoption of bleeding reduction strategies (i.e., radial access or use of ultrasonography- or fluoroscopy-guided vascular access, micropuncture needle technique and vascular closure device if femoral access is used, careful dosing of additional adjunctive antithrombotic therapy), uninterrupted OAC may represent a reasonable approach for patients undergoing PCI. Implementing standardized catheterization laboratory protocols may be of aid in providing guidance and enhancing safety. Nevertheless, further studies with granular data collection are needed to adequately answer which is the optimal antithrombotic management for patients on long-term OAC who are in need of coronary invasive procedures.

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