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'Simple' Way to Stop, Restart DOACs for Surgery in Patients With Atrial Fib

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A proposed strategy aims to fill a glaring hole in the guidelines, which lack evidence-based recommendations for anticoagulation management in patients with atrial fibrillation (AF) undergoing elective surgery in the age of direct oral anticoagulants (DOACs).

The strategy, tested in a 3000-patient cohort study, doesn't call for perioperative heparin bridging or testing of clotting function, but it does lay out a basic schedule for stopping and restarting DOACs based on the type of surgery.

Although the timing of DOAC withdrawal is somewhat tailored case by case, "the overarching approach was to keep it as simple as possible, so it's easy for doctors and patients to follow," James D. Douketis, MD, McMaster University and St Joseph's Healthcare Hamilton, Ontario, told *theheart.org* | *Medscape Cardiology.*

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study was published in the November 2019 issue of *JAMA Internal Medicine* with Douketis as lead author.

Its idea, he said, is to stop the DOAC one day before a procedure considered low-risk for major bleeding and to resume it one day afterward; and to withdraw the DOAC two days before and resume two days after surgeries that are high-risk for major bleeding. Both intervals are based on the DOAC half-lives once administered.

The plan was associated with only about a 2% rate of perioperative major bleeding and less than 1% rate of thromboembolic events in the study's patients on long-term therapy with dabigatran (*Pradaxa,* Boehringer Ingelheim), rivaroxaban (*Xarelto,* Bayer), or apixaban (*Eliquis,* Pfizer/Bristol-Myers Squibb) for nonvalvular AF.

"In some ways, it's validating what a lot of clinicians are doing already," Douketis said. "So some clinicians may feel comfortable with the protocol as it is, especially when you look at the residual [DOAC] blood levels in these patients, which were pretty low. Others may not."

Still, he said, "I think we probably need some more validation in the high-bleeding-risk group, which constituted about a third of the patient population."

The proposed DOAC interruptions schedules are largely consistent with but exceed recent recommendations in the literature, including a 2017 "expert consensus decision pathway" from the American College of Cardiology.

Douketis called those "a good step forward, but they really were not informed by what we think of as high-quality evidence, and a lot of it was expert opinion."

Indeed, current recommendations "are largely based on subgroup analyses of large trials, small studies, or studies that look at a single agent. I think the beauty of this study is that it brings a well-designed, systematic, standardized approach, without heparin bridging," Renato D. Lopes, MD, PhD, Duke Clinical Research Institute, Durham, North Carolina, told *theheart.org* | *Medscape Cardiology.*

PAUSE is a prospective study that tests an approach "we really didn't have strong data to support but is what several other documents recommend." And one of its other strengths, he said, is that it tested patients right before surgery for residual DOAC blood levels.

Virtually all patients showed no or only minimal residual levels during the surgery, the report notes. And 90% to 97% of patients, depending on the DOAC, and 98.8% of all patients undergoing high-bleed-risk surgeries had such low or undetectable levels.

Those findings are the "mechanistic confirmation" of the clinical outcomes that were the study's main focus, said Lopes,

who isn't connected with the research. "They explain why the strategy works."

He agreed that the proposed strategy may be less strongly verified for patients at high bleeding risk. Even the current study's patients categorized as high risk for bleeding "were not at extreme high risk, per se." Baseline modified HAS-BLED scores overall did not exceed 2.0 for the apixaban, dabigatran, and rivaroxaban groups.

"In general the results are very consistent, but I think we have a little more confidence in patients who are not in the extreme of high risk for bleeding," he said. "Those were not so well represented in this study."

The analysis prospectively followed 3007 adult with AF who use apixaban, dabigatran, or rivaroxaban and were slated for an elective surgery at 23 centers, mostly in Canada but also the United States and Europe, from 2014 to 2018, the report notes. Their mean age was about 72 years; two thirds were men.

Prior to their procedure, patients were assigned to low-bleed-risk and high-bleed-risk groups. Low-bleed-risk procedures in two thirds of the patients included colonoscopy and similar gastrointestinal diagnostic procedures, cardiac device implantations, catheter ablations, coronary angiography by radial access, tooth extraction and root canals, skin biopsies, and eye lens implantation for cataracts.

High-bleed-risk procedures in the remaining third of patients included most neurologic procedures and cancer, reconstructive, and other major surgeries.

Participating clinicians received some guidance on how to classify procedures as high or low risk for major bleeding. But because no formal validated classification scheme exists, Douketis noted, "it was left to the physicians' discretion how to classify patients."

The predefined safety standard for arterial thromboembolism — defined as stroke, systemic embolism, or transient ischemic attack — was a rate of 0.5% with an upper 95% confidence interval (CI) that excluded a rate of 1.5% by intention to treat (ITT). All three DOACs met that benchmark.

Only dabigatran, a direct thrombin inhibitor, met the corresponding safety standard for major bleeding, which was 1% with an upper CI that excluded a 2% rate by ITT. The factor Xa inhibitors apixaban and rivaroxaban missed the benchmark, although barely in the case of apixaban, Douketis noted.

Table 1. ITT 30-Day Outcome Rates by DOAC Group in PAUSE, % (95% CI)

End Point	Apixaban (n = 1257)	Dabigatran (n = 668)	Rivaroxaban (n = 1082)
Arterial Thromboembolism[a]	0.16 (0 - 0.48)	0.60 (0 - 1.33)	0.37 (0 - 0.82)
Major Bleeding	1.35 (0 - 2.00)	0.90 (0 - 1.73)	1.85 (0 - 2.65)

[a]Stroke, systemic embolism, or transient ischemic attack

In an analysis only of the majority of patients who actually followed the DOAC-interruption protocol, "people in the apixaban group now qualified as satisfying our statistical measure of safety, in that the upper bound of the confidence interval was less than 2," he said.

Table 2. Per-Protocol 30-Day Outcome Rates by DOAC Group in PAUSE, % (95% CI)

End Point	Apixaban (n = 1079)	Dabigatran (n = 599)	Rivaroxaban (n = 946)

Arterial Thromboembolism[a]	0.19 (0 - 0.56)	0.50 (0 - 1.25)	0.42 (0 - 0.94)
Major Bleeding	1.2 (0 - 1.89)	1.0 (0 - 1.93)	1.69 (0 - 2.53)

[a]Stroke, systemic embolism, or transient ischemic attack

Whether the two factor Xa inhibitors were "safe" in the current study depends largely on perspective, whether that of a statistician or a clinician, Douketis proposed.

Only dabigatran met the prospectively defined safety criteria for major bleeding, but the apixaban numbers satisfied those criteria in the per-protocol analysis. And, he noted, none of the differences among agents may be all that clinically meaningful.

"It depends on what hat you wear," he said. "Clearly the rates of major bleeding were not widely different from what was expected. They were numerically less than 2%. Having said that, the study was not designed to compare bleeding rates across the three groups."

The study's numbers were small, there was little variation among the three agents, and their differences from predicted outcomes were "really minor," Lopes agreed.

"All three DOACs were pretty similar across the board in terms of low-bleeding risk, low ischemic risk, and fulfilling the strategy that was proposed."

Edoxaban (*Savaysa,* Daiichi Sankyo) wasn't part of the analysis because it had yet to be approved when the PAUSE study launched, so "the results are not generalizable to this DOAC," the report notes.

Douketis disclosed personal fees from Pfizer, Sanofi, Leo Pharma, Bristol-Myers Squibb, Janssen, The Merck Manual, and UpToDate "outside of the submitted work." Disclosures for the other authors are in the report. Lopes disclosed research grants from Bristol-Myers Squibb, Pfizer, Amgen Inc., GlaxoSmithKline, Medtronic PLC, and Sanofi Aventis; and consulting fees from Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, and Bayer AG.

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