Measuring direct oral anticoagulants—when, how

Amy Carpenter Aquino

January 2022—Laboratories don't have to monitor direct oral anticoagulants, but they might want to measure DOAC drug levels in some situations in some patients, said Karen A. Moser, MD, associate professor of pathology, University of Utah Spencer Fox Eccles School of Medicine, and medical director of the hemostasis/thrombosis laboratory at ARUP Laboratories, in a CAP21 session. She and others reported what those situations are, 2021 recommendations, CAP proficiency testing findings, DOAC effect on coagulation assays, and cases from their practices.

"Clinical trials evaluating these drugs described expected on-therapy concentrations for each of the drugs—dabigatran, the direct thrombin inhibitor, and three direct Xa inhibitors," she said, referring to rivaroxaban, apixaban, and edoxaban.

In the clinical trial cohorts, expected peak and trough ranges were described for each of the four DOACs in patients treated for deep vein thrombosis and pulmonary embolism, and collated in the 2018 International Council for Standardization in Haematology recommendations for laboratory measurement of DOACs, with an update to the recommendations published in 2021 (Gosselin RC, et al. *Thromb Haemost.* 2018;118[3]:437–450 and Douxfils J, et al. *Thromb Haemost.* 2021;121[8]:1008–1020). "That at least gives us something to compare with in the literature if we choose to make a measurement of any of the DOACs while a patient is on therapy," Dr. Moser said. "If we make a random measurement, it's hard to know what that number might mean. We can't compare it with a peak or a trough" and are left wondering if the number means the patient is sufficiently anticoagulated.

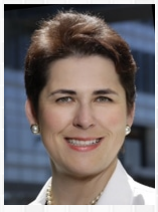
DOACs have a yearly risk of one to three percent for major bleeding and one to two percent for thromboembolic events, said co-presenter Oksana Volod, MD, director of coagulation and associate professor of pathology and laboratory medicine at Cedars-Sinai Medical Center, Los Angeles.

"Several studies demonstrated there is a dose-response relationship between DOAC concentrations and those adverse events," Dr. Volod said. "Thromboembolic events, as well as strokes, mainly occurred in patients with the lowest trough levels, whereas high trough levels were associated with a higher risk of major bleeding." It is likely that patients could further benefit from tailored DOAC therapy, in particular special patient populations, such as those with extremely high or low body weight, impaired kidney function, or prior intestinal surgery, and in specific clinical situations—for example, patients who restart anticoagulation after a major bleeding or who experience a thrombotic event while on DOAC therapy (Toorop MMA, et al. *J Thromb Haemost.* 2020;18[12]:3163–3168).

Dr. Volod cited the key recommendations from the 2021 update of the International Council for Standardization in Haematology consensus on laboratory measurement of DOACs:

- There are insufficient data to date for providing dose-adjustment recommendations based on DOAC levels alone.
- Nevertheless, DOAC measurements may identify potential excessive clearance or drug accumulation and could be used in situations where the benefit of such measurement is likely to outweigh the risk, for example, in nonurgent situations.
- If a DOAC measurement has been requested for urgent purpose, results should be provided within 30 minutes to aid in acute clinical decision-making.

Meeting the 30-minute recommendation may not be feasible, Dr. Volod said. The Cedars-Sinai laboratory offers apixaban and rivaroxaban levels 24/7, but "specimen drawing and delivery especially can take several minutes, so results may not be available within 30 minutes."



Dr. Volod

The possible indications for DOAC testing in nonurgent situations, according to the ICSH, are advanced age, severe renal failure and dialysis dependence, high bleeding risk interventions, and a BMI above 40 kg/m^2. For patients with a BMI less

than 40 or weight less than 120 kg, any DOAC can be used, but for patients above those levels, rivaroxaban or apixaban are the preferred drugs. “And no monitoring is indicated because of the lack of available safety and efficacy data,” Dr. Volod said. Another nonurgent indication for DOAC testing would be in a case of a possible drug interaction.

The urgent situations are those of acute bleeding and where appropriate reversal strategies have to be determined.

In the perioperative setting, the American Society of Regional Anesthesia and Pain Medicine 2015 guidelines suggest that DOAC interruption be based not only on their respective half-lives but also on residual drug concentration. “In this situation,” Dr. Volod said, “to accurately measure low plasma drug concentrations, we recommend that laboratories have to have assays, Xa assays, calibrated for the assessment of low plasma concentrations,” for example, less than 50 ng/mL^{-1} (Douketis JD, et al. *Reg Anesth Pain Med.* 2016;41[2]:127–129).

In emergency situations (bleeding, thrombosis, urgent invasive procedure, thrombolysis), “we potentially can assess if DOAC is present and how much,” Dr. Volod said. “The aim would be to identify a level within or above the on-therapy range to guide the potential use of specific reversal agents or at least identify if a drug is there.” DOAC antidote administration is warranted if the drug concentration is greater than 30 ng/mL^{-1} in patients requiring an urgent intervention, according to International Society on Thrombosis and Haemostasis guidelines. In patients with serious bleeding, antidote administration should be considered if the drug concentration exceeds 50 ng/mL^{-1} (Levy JH, et al. *J Thromb Haemost.* 2016;14[3]:623–627).

The CAP Hemostasis and Thrombosis Committee, of which Dr. Volod is a former member, recently reported 2013–2016 Survey data on the measurement of rivaroxaban and dabigatran (Volod O, et al. *Arch Pathol Lab Med*. Epub ahead of print June 16, 2021. doi:10.5858/arpa.2020-0633-CP), including the effect of those drugs on coagulation assays such as PT, aPTT, and thrombin time. “As published in the literature,” Dr. Volod said, “aPTT is not very sensitive to direct Xa inhibitors and it is insensitive to apixaban.”

“There is significant variability between reagents,” she said, noting that the three most common instrument-reagent combinations reported in the Survey were those of Diagnostica Stago, Instrumentation Laboratory (now Werfen), and Siemens Healthineers. “The most sensitive in terms of aPTT was the IL reagent showing abnormal results for aPTT and rivaroxaban,” she said. Rivaroxaban aPTT results were measured at concentrations of 50, 200, and 400 ng/mL, and the aPTT reagents were more responsive to rivaroxaban concentration in the 200–400 ng/mL range. aPTT was reported as prolonged by 92 percent of participants for 200 ng/mL and by 94 percent of participants for 400 ng/mL.

In an earlier study of patients treated with DOACs, Dr. Volod said, prothrombin time was somewhat more sensitive to direct Xa inhibitors (rivaroxaban, edoxaban, apixaban). Rivaroxaban showed the strongest effect on PT, followed by edoxaban and then apixaban (Douxfils J, et al. *J Thromb Haemost.* 2018;16[2]:209–219).

In the CAP Survey, the prothrombin time was more responsive to rivaroxaban. At the 50 ng/mL rivaroxaban concentration, 49.6 percent of participants reported normal prothrombin time results, but PT was reported as prolonged by 98.7 percent of participants for the 200 ng/mL rivaroxaban concentration and by 100 percent of participants for the 400 ng/mL rivaroxaban concentration. The Diagnostica Stago Neoplastin CI Plus reagent appeared to be the most sensitive to rivaroxaban across all three drug concentrations.

“There was insufficient sensitivity, even if paired with a normal aPTT, to completely exclude DOAC presence,” Dr. Volod said.

Table 1.
DOAC—assay choices for measurement

LC/MS

- Considered gold standard for quantification
- Reportable range 5–500 ng/mL
- Only available in small number of reference laboratories
- No international reference standard available
- Timing of measurement matters
- Prefer peak or trough instead of random

DOAC-specific anti-Xa

- Classified as research use only
- Classified as a laboratory-developed test for clinical use; requires local validation

- Timing of measurement matters
- Prefer peak or trough instead of random

DOAC-specific DTI

- Dilute thrombin time
- Ecarin-based assays

Other

- Anti-Xa level calibrated for UFH/LMWH
- PT/PTT
- Thrombin time
- TEG
- Use qualitative tests with caution

Douxfils J, Ageno W, Samama C-M, et al. *J Thromb Haemost.* 2018;16[2]:209–219.

Nearly 50 percent of participants reported that the prothrombin time was not prolonged with a 50 ng/mL rivaroxaban concentration, "again highlighting that with the normal PT, we cannot exclude drug presence," Dr. Volod said.

"This supports the [2018] ICSH consensus screening recommendations that PT and aPTT may not be reliable to detect the presence of on-therapy concentration of all DOACs," she said. They are not responsive to on-therapy apixaban level, and they should not be used to quantify DOAC concentration. In a patient with known DOAC exposure, a prolonged PT or aPTT should be considered secondary to drug effect until proven otherwise, according to the recommendations. The recommendations also say that in emergent or life-threatening conditions, tests for quantifying DOAC should be performed to aid in managing the patient. "A normal thrombin time will exclude the presence of significant dabigatran concentration," Dr. Volod said, referring to the recommendations. "And nonspecific point-of-care testing methods, like PT, aPTT, and activated clotting time, may not have sufficient responsiveness to detect DOAC presence and should not be used for those purposes" (Gosselin RC, et al. *Thromb Haemost.* 2018;118[3]:437–450).

The use of viscoelastic assays in DOAC measurement does not hold much promise because they are not sensitive enough to DOAC effects, Dr. Volod said. "They are more sensitive to dabigatran because the activator is kaolin in the majority of those assays and they are least sensitive to rivaroxaban and apixaban." The ICSH consensus recommendation in 2018 said that at that time, there was not enough clear data to support the use of TEG or ROTEM for detecting DOAC anticoagulant activity.

Amanda M. VanSandt, DO, medical director of the hemostasis and thrombosis service, Oregon Health and Science University, and associate professor of pathology and laboratory medicine, OHSU School of Medicine, set out the assay choices for DOAC measurement (**Table 1**). Laboratories with a more routine volume of cases, she said, should favor validating an on-site quantitative DOAC assay for accurate and timely results. "Actual measurements of concentration would be most useful, such as the LC/MS method or a DOAC-specific calibrator with an anti-Xa assay." Laboratories that don't have quantitative DOAC assays on site should consider send-out testing for quantitative measurements. However, laboratories that don't have a validated quantitative assay locally and cannot await send-out testing, such as in emergencies, should consider the use of a qualitative assay to assess for DOACs, such as routine clotting time or perhaps a heparin-specific assay, she said.

Qualitative assays, such as anti-Xa activity calibrated for unfractionated or low-molecular-weight heparin, could be considered useful in an emergent situation, Dr. VanSandt said, "though these have to be used with caution because heparin and the anti-Xa DOAC act in the same mechanism or at the same time in the coagulation cascade. This means that anti-Xa assays calibrated for unfractionated or low-molecular-weight heparin will likely turn positive in the setting of a DOAC once the medication reaches a certain concentration within the sample."

At least one study suggests that using anti-Xa assays calibrated for UFH and LMWH could detect significant levels of DOAC (Gosselin R, et al. *Int J Lab Hematol.* 2016;38[5]:505–513), though others suggest response may vary by kit (Sabor L, et al. *Thromb Res.* 2017;156:36–38).

Dr. VanSandt

“If you’re using this type of method in your hospital or laboratory, we want you to make sure you understand how these DOACs are affecting the assay in your hand,” she said.

Laboratories would welcome anti-Xa chromogenic assays with DXa-inhibitor-specific calibrators, Dr. VanSandt said, and a limited number of FDA-approved calibrator materials are now available. These assays can measure a wide range of concentration of the DOACs, and just as the DOACs can make the heparin-calibrated assays positive, heparin can make the DOAC-calibrated assays positive. “So it would be useful to optimize your laboratory information system to detail what anticoagulant is being used by the patient so the lab can use the correct calibrator on the assay.”

A proposed novel testing strategy using a urine dipstick assay (DOAC Dipstick, Doasense GmbH, Germany) for DOAC detection has been tested in small trials, Dr. VanSandt said, explaining, “Because these medications are renally cleared, a urine assay is possible to detect the different DOACs.” Results from an interlaboratory study of seven participants showed the dipstick is fairly sensitive for apixaban, rivaroxaban, and dabigatran and “pretty specific for the drug involved,” she said (Harenberg J, et al. *Semin Thromb Hemost.* 2019;45[3]:275–284).

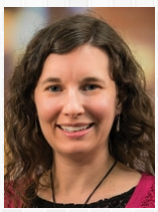
Drs. Volod and Moser presented clinical cases they encounter in practice, ones in which DOAC measurement could be helpful even though lab monitoring isn’t required. The first was of an aPTT and heparin assay discrepancy in a patient admitted to the hospital while on apixaban and then switched to unfractionated heparin.

At Cedars-Sinai, the method of measuring heparin effect is a heparin level by anti-Xa assay, Dr. Volod said. When the patient was switched to unfractionated heparin, the anti-Xa assay was showing a supratherapeutic heparin level. The value of the therapeutic level is 0.3 to 0.7 IU/mL, and the patient’s values ranged from 1.94 to 2.20 IU/mL. The clinicians stopped the heparin, and the case was brought to Dr. Volod’s attention. The patient was stable. She added to the workup, in addition to the anti-Xa assay, aPTT (normal, 35 sec), PT (elevated, 20.7 sec), and fibrinogen (elevated, 522 mg/dL). Since PT reagents have heparin neutralizers in them, PT usually will not be normal if a patient is on even a therapeutic heparin dose, she said, so the high PT value of 20.7 seconds “was another clue that the patient was still having a residual effect of apixaban.”

Based on those results, “it immediately came to my attention that most likely we still experienced the DOAC Xa-inhibitor apixaban effect on coagulation assays, such as unfractionated heparin as well as PT,” Dr. Volod said. She recommended continued patient monitoring with aPTT rather than an anti-Xa level. The heparin was restarted, and aPTT, which was steadily rising, was used for monitoring.

Depending on renal function, in the first 24 to 36 hours—and in Dr. Volod’s experience, even after several days up to one week—DOAC still can have an additive effect on the screening assays, she said. “Therefore, laboratories should be able to provide alternative strategies for assessing heparin anticoagulation.”

Dr. Moser presented a case similar to though not the same as Dr. Volod’s case, and it’s representative of the following situation she’s encountered: A physician calls the lab because they have a patient switching from rivaroxaban (or another direct Xa inhibitor) to LMWH. They want to use the lab’s anti-Xa assay calibrated for LMWH to monitor LMWH during the transition. They ask, “Will rivaroxaban interfere with the test?”



Dr. Moser

Just as in Dr. Volod’s case, the anti-Xa activity assay—the underlying parent assay—is the same, whether the laboratory

calibrates it to measure UFH, LMWH, or rivaroxaban, Dr. Moser said. And it can pick up the effects of any or all of those. "So this is a sticky situation. It's challenging to provide laboratory monitoring when we're transitioning from these DOACs to one of the heparins if we want to make laboratory measurements."

It's easier with dabigatran, she said, because dabigatran is a direct thrombin and does not interfere with anti-Xa activity assays. "The direct Xa inhibitors cause the issue."

Another case centered on the potential utility of viscoelastic assays. In this case, a patient with a fall was transferred to Cedars-Sinai for a higher level of care. "We knew the patient took rivaroxaban within 24 hours of admission and received a dose of Kcentra [prothrombin complex concentrate]," Dr. Volod said.

Physicians first performed a thromboelastogram (TEG) on this patient and said the results looked normal. Though the point of the case was not to discuss TEG parameters, Dr. Volod noted that the R parameter will affect the coagulation factor, "so anything that affects coagulation factors will potentially affect the R parameter," she said. In case of factor/s deficiency or anticoagulant effect, R will be prolonged. In this case R was shortened, indicating an increased rate of thrombin generation. The patient also received thrombin concentrate, which also could potentially affect that parameter. The physicians asked, "Is it safe to take the patient to surgery, and is there a DOAC effect or not?"

Dr. Volod added a workup to measure PT, aPTT, and UFH level; she didn't include an anti-Xa assay because Cedars-Sinai didn't have apixaban or rivaroxaban assays at that time. (They were brought in-house because of this case and similar cases.) aPTT was normal; PT was above the reference range. UFH "showed a level [1.90 IU/mL] that potentially would be supratherapeutic, but we cannot apply this to the level for Xa inhibitors," Dr. Volod said. "We can just say, 'Based on these parameters, there is still the effect of rivaroxaban present.'"

Regarding Xa inhibitors, Dr. Volod raised three points. First, "we have to remember the viscoelastic assay main activator is kaolin, which is a contact surface activator that activates assays for aPTT and activated clotting time. And that is the reason the R parameter of TEG or the Intem parameter of ROTEM will be closer to the aPTT rather than PT and that abnormal clotting time may not exclude Xa inhibitor presence." In this case the R was shortened, "and that can be misleading information," she said.

Second, PT sensitivity is drug and reagent dependent. "In our institution, we use the Stago reagent and instruments, and based on personal experience and published literature, I know the sensitivity of the reagent we use in our laboratory." Pathologists need to be aware of the sensitivity of their reagents to the different DOAC levels, she said.

Third, the unfractionated heparin and low-molecular-weight heparin anti-Xa assay can be used to detect or exclude drug presence. "By anti-Xa method, we can detect the presence of the drug but not the level of the drug," she said. "For this you need an Xa assay calibrated with apixaban and rivaroxaban" (Billoir P, et al. *Ann Pharmacother.* 2019;53[4]:341–347).

The following two cases highlight the potential interference of DOACs in other hemostasis and thrombosis laboratory tests.

In one case, a 54-year-old woman had been bedridden while treated for pneumonia. During her recovery, Dr. Moser said, she developed a PE, which prompted testing for lupus anticoagulant, among other things.

A DRVVT-based and an aPTT-based lupus anticoagulant test, both with screening, mixing, and confirmatory components as per current ISTH recommendations, were used. The PNP test used is a platelet neutralization procedure—an aPTT-based lupus anticoagulant confirmatory assay.

The patient's PT result was prolonged (23 sec, RI 12.0–15.3 sec), "and that's a little curious for a few reasons," Dr. Moser said. One is that reagents tend to have a very high phospholipid concentration, "so we don't typically expect lupus anticoagulants to prolong the PT to any significant degree," she said. "Anytime I see that my radar is up, thinking about what else could be present in this patient plasma sample that's causing that PT to be prolonged." Lupus anticoagulant wouldn't typically do that, she said, "so I'm wondering if something else is going on, and specifically if there's an anticoagulant present."

The DRVVT screen was prolonged (57 sec, RI 33–44 sec), "and there's an inhibitory pattern that the mixing study doesn't completely correct into our reference interval. But when we added back an increased phospholipid concentration in the DRVVT reaction, we weren't able to demonstrate phospholipid dependence of this apparent inhibitor. So our confirmatory test came up as negative."

The aPTT screen was also prolonged (61 sec, RI 32–48 sec). "Anytime we see prolonged aPTT screens we always wonder: Could this be heparin? A lot of us who work in thrombosis-hemostasis laboratories are conditioned to be suspicious for heparin, whether it's heparin that's therapeutic and expected to be present or heparin from a hep-lock IV line, or if there's a line draw that wasn't adequately flushed." Thrombin time was normal, suggesting no presence of heparin or a direct thrombin inhibitor.

The aPTT-based mixing study “nearly but not completely” corrected (49 sec, RI 32–48 sec).

“In our initial aPTT confirmatory test, the platelet neutralization procedure also was negative,” she said. Another aPTT-based confirmatory test—hexagonal phospholipid neutralization—came up positive.

“Overall, this prolonged PT is kind of suspicious, making us think there could be some sort of drug present,” Dr. Moser said. “And it turned out there was.”

At the time the patient was tested, she was receiving rivaroxaban for her PE, and Dr. Moser suspected it was that causing the prolonged PT in their instrument-reagent system. “It also calls into question the lupus anticoagulant results” as potential false-positives.

The laboratory tested a follow-up specimen from the patient about 12 weeks later, for which her physician opted to pause the patient’s anticoagulant therapy. “Lo and behold, her PT was completely normal, as were her DRVVT and aPTT screens,” Dr. Moser said. “So that throws these initial results into question.”

While it’s possible the patient had a transient lupus anticoagulant detected initially and gone within 12 weeks, “the more likely scenario, given the clinical correlation, knowing that rivaroxaban was present initially, knowing that our prothrombin time was prolonged initially, is that the apparent lupus anticoagulant result we were picking up was likely an effect of the direct Xa inhibitor.”

Dr. Moser shared the next case for “contrast.” A 37-year-old man with an unprovoked PE underwent laboratory evaluation for various causes of thrombophilia, including lupus anticoagulant. This patient’s PT was normal, so there’s no clue of drug interference. His DRVVT screen was prolonged (91 sec, RI 33–44 sec). The mixing study remained prolonged (80 sec, RI 33–44 sec), “so it looked like an inhibitor effect,” she said. The DRVVT confirmatory test was also positive, and the aPTT screen was prolonged (119 sec, RI 32–48 sec).

The lab checked for heparin or direct thrombin inhibitor with thrombin time, which was normal, “so it doesn’t look like either heparin or direct thrombin inhibitor is present,” she said.

The aPTT mixing study didn’t correct (85 sec, RI 32–48 sec), “and our aPTT confirmatory assay, the platelet neutralization procedure, also looked positive,” Dr. Moser said.

Discussion with the ordering physician revealed that the patient had been on apixaban at the time of testing. “As Dr. Volod showed us, PTs are relatively insensitive to the presence of apixaban, and that was the case for our reagent in my laboratory.”

Of the lupus anticoagulant results, she asked, “Can we trust them in the presence of a direct Xa inhibitor?”

“It’s interesting that both the DRVVT and the aPTT-based testing came up as positive.” To be certain there’s no drug interference causing false results, it would be optimal, if possible, she said, to test while this patient is on low-molecular-weight heparin, if he transitions for a short time, or in the absence of anticoagulant if it would be safe to do so. There has also been work looking at drawing lupus anticoagulant samples at expected drug trough, Dr. Moser said. “So when the lowest level of, in this case, apixaban is present, to try to minimize interference. That could be another strategy.”

Dr. Moser requested but did not receive a follow-up sample from this patient to investigate whether lupus anticoagulant was present, so no follow-up data are available. But she contrasted this case with the prior case involving rivaroxaban in which the PT was prolonged. “As Dr. Volod showed, there’s significant variability, so understanding the performance expected from your PT and aPTT reagents is key to being able to interpret results in your laboratory.”

Table 2 sums up DOAC laboratory test interference, and Dr. Moser noted a few themes. “Rarely, false-negative results with lupus anticoagulants have been reported, mostly in the context of apixaban. That might be another point in favor of a potential real lupus anticoagulant” in the case of the 37-year-old male patient. In addition, PT- or aPTT-based factor assays can be falsely underestimated. And DOACs can interfere, too, in measurements of the natural anticoagulants antithrombin, protein C, and protein S. “In protein C and protein S activity, we’re expecting false overestimations with clot-based assays, so we run the risk of misclassifying a truly deficient patient as having a normal protein C or protein S level.”

Table 2. DOAC—laboratory interference

Assay	Direct thrombin inhibitor	Direct Xa inhibitor
aPTT	Prolonged ↑↑	Prolonged ↑
PT/INR	Prolonged ↑	Prolonged ↑↑
Thrombin clotting time	Prolonged ↑↑↑	No effect
Antithrombin activity a. Factor Xa-based b. Factor IIa-based	 a. No effect b. Falsely overestimated	 a. Falsely overestimated b. No effect
Protein C activity a. Clot-based b. Chromogenic	 a. Falsely overestimated b. No effect	 a. Falsely overestimated b. No effect
Protein S activity a. Clot-based b. Free protein S antigen	 a. Falsely overestimated b. No effect	 a. Falsely overestimated b. No effect
aPTT-based activated protein C resistance with added factor V deficient plasma	Falsely elevated ratio	Falsely elevated ratio
aPTT-based factor assays	Falsely low factor VIII, IX, XI	Falsely low factor VIII, IX, XI
PT-based factor assays	Falsely low factor II,V, VII, X	Falsely low factor II, V, VII, X
Chromogenic factor VIII activity	No effect	Falsely low
aPTT mixing study	Incomplete correction	Incomplete correction
PT mixing study	Incomplete correction	Incomplete correction
Lupus anticoagulant tests	Possible to misclassify as LA	Possible to misclassify as LA, rarely may give false-negative for LA*

↑ = slight increase; ↑↑ = moderate increase; ↑↑↑ = marked increase

Hollensead S, Krishnan J, Kottke-Marchant K. Coagulation testing. In: Kottke-Marchant K. *An Algorithmic Approach to Hemostasis Testing.* 2nd ed. College of American Pathologists; 2016:71–98.
*Favaloro EJ, et al. *Pathology.* 2019;51(3):292–300.

Chromogenic protein C activity assays are not subject to this type of DOAC interference, she said, and free protein S antigen (or total S antigen) would show no effect from DOACs.

Antithrombin activity assays deserve special mention, she said, because the underlying assay design—whether factor Xa or IIa based—determines which of the DOACs could potentially interfere.

"Let's take the case of direct Xa inhibitors," Dr. Moser said. "If the antithrombin activity is factor Xa based, there's a potential to overestimate antithrombin activity in the presence of a direct Xa inhibitor. But if the antithrombin activity is factor IIa based, we wouldn't expect the direct Xa inhibitor to have a significant interfering effect. And that's reversed for direct thrombin inhibitors."

A few examples of hemostasis and thrombosis tests that are unaffected by DOACs are ELISA or latex immunoassay-based tests, such as D-dimer and von Willebrand antigen; DNA-based tests, such as those measuring prothrombin G20210A or factor V Leiden mutation; and fibrinogen activity using the Clauss method (Mani H. *Int J Lab Hematol.* 2014;36[3]:261–268; Gosselin RC, et al. *Thromb Haemost.* 2018;118[3]:437–450).

With the years of experience with heparin neutralization in the clinical laboratory, using compounds like heparinase or polybrene, one could ask, why not just neutralize the DOAC also?

The answer lies in an area of active investigation "not ready for prime time," Dr. Moser said, "but there's a growing body of literature in which laboratories are sharing their initial experiences. And this is something to keep an eye on in the coming years" (Siriez R, et al. *Int J Lab Hematol.* 2021;43[1]:7–20; De Kesel PM, et al. *J Thromb Haemost.* 2020;18[8]: 2003–2017; Platton S, et al. *Int J Lab Hematol.* 2019;41[2]:227–233; Jilma-Stohlawetz P, et al. *Int J Lab Hematol.* 2021;43 [2]:318–323).

Two DOAC-neutralizing strategies—DOAC-Stop (Haematex Research, Australia) and DOAC-Remove (5-Diagnostics AG, Switzerland) are tablet-based compounds that incorporate activated carbon. DOAC Filter (Diagnostica Stago, France) is a filtration system. None of these is FDA approved, Dr. Moser said, and each assay has manual steps. "This would require careful consideration of how it would fit into a laboratory workflow." And then there's the added cost for the additional reagent and the time, and the possibility of needing additional patient plasma.

As for whether the strategies work, the preliminary, limited data "is promising," Dr. Moser said. "Those neutralizing compounds appear to decrease interference in lupus anticoagulant testing, as well as some selected factor assays,

activated protein C resistance, and antithrombin activity, based on data that have been published to date."

Some groups report that DOAC-Stop can cause decreased factor activities in treated plasmas, she said, "so there is a question whether we are inadvertently absorbing some factors that we don't mean to in addition to the direct oral anticoagulants." The data are mixed, she said, but it's a question worth considering: "Are we inadvertently taking something else out?"

"It's an area wide open for investigation," she said.

Amy Carpenter Aquino is CAP TODAY senior editor.