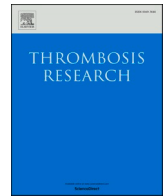


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# Thrombosis Research

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## Editorial

### DOAC drug levels: Does “knowing” lead to safer care?



Since they were first introduced, the four commonly used direct oral anticoagulants (DOACs) have been marketed as fixed-dose medications. In essence, there is one “correct” dose for a patient based on the indication, their ability to metabolize the medication (some combination of renal function, liver function, body weight, and age), and any potential drug-drug interactions. As such, DOACs differ significantly from vitamin K antagonists (e.g., warfarin) as their drug levels and doses are not continuously monitored and adjusted. However, many clinicians feel the need to check DOAC drug levels in certain clinical situations. When this testing is performed and how it impacts clinical care is the focus of a clinical study by Cavaillez and colleagues.

In this study, the investigators collected data from 1488 patients at a single center in France who underwent 2197 DOAC drug level measurements. Drug level assays were drawn primarily for apixaban and rivaroxaban, with a range of 1–13 levels per patient (26% of patients had multiple drug levels drawn). These were drawn primarily prior to emergent procedures (32%), elective procedures (17%), in the setting of acutely changing renal function (13%), suspicion of ischemic stroke (11%), or bleeding events (14%). While the prothrombin time did correlate with rivaroxaban drug levels, no standard coagulation test sufficiently correlated with apixaban drug levels. Among the nearly 2200 DOAC drug levels, 49% lead to a clinical decision, including proceeding with or intentionally delaying an invasive procedure. One notable finding is that a last intake of DOAC two or more days prior resulted in undetectable drug levels in a high proportion of patients (sensitivity 85%, specificity 74%).

Both the International Society on Thrombosis and Haemostasis (ISTH) and American College of Cardiology (ACC) describe the importance of DOAC levels in the setting of emergent reversal for bleeding [1,2]. In this scenario, drug levels can be useful in determining the ongoing contribution to bleeding and the need to administer a reversal agent. The clinical utility of DOAC drug levels outside this setting is an area of debate. General guidance has been to avoid obtaining levels for the purposes of assessing drug effect or only to do so in the rare instances where multiple factors may interfere with DOAC pharmacokinetics [3,4]. However, this practice has still been described with some frequency in the literature, present study included.

An important finding from the study by Cavillez et al. is the strong association between time since last dose and drug levels. In this report, a last DOAC intake of two or more days prior resulted in no detectable drug level in the vast majority of patients. These results largely mirror the experience from the Perioperative Management of Patients with Atrial fibrillation Receiving a Direct Oral Anticoagulant (PAUSE) study [5]. In that multi-arm prospective study, patients on chronic DOAC therapy who were scheduled for an invasive procedure used a pre-set management protocol for holding anticoagulant therapy before their procedure. Patients on chronic apixaban or rivaroxaban therapy who were undergoing low bleeding risk procedures were advised to hold their DOAC for one day pre-operatively while those undergoing high bleeding risk procedures held for 2 days pre-operatively. Among patients who had a  $\geq 48$  h interruption period of apixaban and rivaroxaban, only 10.0% and 18.0% had residual levels  $\geq 30$  ng/mL, respectively [6]. Even fewer (2.1% for apixaban and 0.7% for rivaroxaban) had drug levels  $\geq 50$  ng/mL. Taken together, the PAUSE study and this study by Cavillez and colleagues support the notion that time since last DOAC dose is a strong predictor of residual drug levels and can be reliably utilized without the need for laboratory drug levels in most patients undergoing elective or urgent surgical procedures. As such, up to one-in-six DOAC drug levels could potentially be avoided, as estimated by Cavillez and colleagues.

Concern for altered exposure in stable patients is another common clinical scenario in which DOAC levels are obtained. This accounted for the approximately 20% of levels reported by Cavillez and colleagues that were obtained in stable patients who did not require special intervention. In phase III clinical trials, post-hoc analysis of dabigatran and edoxaban trough levels demonstrated significant association with ischemic and bleeding outcomes [7,8]. For example, Reilly and colleagues describe that a dabigatran trough level of 210 ng/mL doubled the rate of major bleeding compared with a trough of 88 ng/mL and a trough of 28 ng/mL increased the relative risk of stroke by 50% compared with the median trough concentration of 59 ng/mL. Similarly, bleeding outcomes were associated with rivaroxaban and apixaban exposure while efficacy outcomes were not [9–11]. It is possible that the low ischemic event rates in the clinical trials limited the power to detect this association. However, unless grossly abnormal, interpreting levels in “real-world” patients for the purposes of assessing bleeding and thrombotic risk is challenging given the lack of established therapeutic ranges. “On-treatment” values described in Phase II/III trials have been used for clinical context, but most of these patients had normal or only mildly impaired end-organ function, relatively few drug interactions, and likely low overall clinical complexity. DOAC levels obtained due to exposure concerns are typically in high complexity patients with baseline thrombotic and bleeding risk different than that seen in clinical trials. Indeed, retrospective analyses of these trials found patient factors, such as aspirin use, anemia, and prior gastrointestinal bleeding, were as important or stronger correlates of bleeding risk than DOAC exposure. Thus, using levels to make assumptions about clinical risk relative to that seen in clinical trials may be misguided and outcomes associated with targeting specific levels is unknown. Furthermore, the contribution of age and renal function to

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DOAC exposure and risk of adverse events remains to be further characterized [12].

Other factors must be considered when determining the value of DOAC levels. One potential drawback is the baseline cost and implications of waiting to batch tests versus running them as soon as they are clinically requested. Another potential drawback is the length of time it takes for a test to be performed, which may limit its applicability in emergent situations. Third, drug specific DOAC levels are not universally available in all hospital and ambulatory care settings and data justifying the cost-effectiveness and value of such broad availability are lacking. Finally, direct evidence linking drug or drug function levels to clinical outcomes are not always available. For instance, platelet aggregation laboratory tests to tailor the dosing of thienopyridine antiplatelet medications did not improve thrombotic or bleeding outcomes in at least one large, randomized trial [13]. Without prospective effectiveness data, it remains unknown if any benefit would be seen from personalizing DOAC doses to drug effect levels.

At present, the best utility of DOAC levels is in the setting of emergent procedure or bleeding, particularly when the last dose was taken within the preceding 48 h. For patients with end-organ dysfunction, this time frame may need extended to the last several days. There likely is potential to optimize DOAC exposure in patients at high risk for altered metabolism and/or poor outcomes, however this falls outside the current body of literature. Altering exposure through off-label dose adjustments may have unintended consequences on outcomes and cannot be recommended. For example, patients that received an edoxaban dose reduction for concomitant drug interaction in ENGAGE-AF had a relative increase in the risk of stroke and systemic embolism compared to warfarin, so this recommendation was left out of the package labeling. Trials investigating the potential for targeted therapeutic ranges with tailored dosing may be beneficial for high-risk patient populations.

### Declaration of competing interest

SH – none.

GDB – consulting for Pfizer/Bristol-Myers Squib, Janssen, Acelis Connected Health.

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