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Performance of direct oral anticoagulant (DOAC) testing by hemostasis laboratories: The Australasian/Asia-Pacific experience

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Abstract

Introduction: Direct oral anticoagulants (DOACs) reflect anticoagulation agents given to treat or prevent thrombosis, having largely replaced vitamin K antagonists (VKAs) such as warfarin. DOACs are given in fixed daily doses and generally do not need monitoring. However, there may be a variety of reasons that justify measurement of plasma DOAC levels in individual patients.

Methods: We report updated findings for DOAC testing in our geographic region, using recent data from the RCPAQAP, an international external quality assessment (EQA) program, currently with some 40–60 participants in each of the different DOAC (rivaroxaban, apixaban, dabigatran) modules, to assess laboratory performance in this area. Data has been assessed for the past 5 years (2019–2023 inclusive), with 20 samples each per DOAC.

Results: Data shows a limited repertoire of assays in use, and mostly consistency in reported numerical values when assessing proficiency samples. Available assays mostly comprised reagents from four manufacturing suppliers. There was good consistency across what participants identified as 'DOAC detected', but some variability when participants attempted to grade DOAC levels as low vs moderate vs high. Inter-laboratory/method coefficient of variation (CVs) were generally <15% for each DOAC, when present at >100 ng/mL.

Conclusion: We hope our findings, reflecting on mostly consistent reporting of DOAC levels and interpretation provides reassurance for clinicians requesting these measurements, and helps support their implementation in regions where there is a paucity of test availability.

KEYWORDS

anti-thrombin, anti-Xa, apixaban, assay variability, dabigatran, direct oral anticoagulant, DOAC, EQA, external quality assessment, laboratory testing, proficiency testing, rivaroxaban

1 | INTRODUCTION

Anticoagulants represent a class of drugs predominantly used to treat and/or prevent thrombosis.[1,2] The classical anticoagulants comprise the vitamin K antagonists (VKAs) such as warfarin, and the heparins, predominantly unfractionated heparin (UFH) and low molecular weight heparin (LMWH). Since UFH and LMWH represent parenteral agents that need to be administered by injection

(either intravenously [UFH] or subcutaneously [LMWH and sometimes UFH]), they tend to be used mostly in hospital settings and for acute need. In contrast, VKAs (administered orally) have instead represented the historical anticoagulant of choice for extended or long-term treatment. In the mid 2010's, a separate class of anticoagulants, namely the direct oral anticoagulants (DOACs), were developed; these have favourable efficacy and safety compared to the classical anticoagulant agents. These comprise two separate classes, being direct anti-thrombin (anti-IIa; dabigatran) or direct anti-Xa (rivaroxaban, apixaban, edoxaban, etc) agents.[1–4] The classical anticoagulants, UFH and VKAs, require regular laboratory monitoring, using the activated partial thromboplastin time (APTT)[5,6] or anti-factor Xa assay (for heparin)[6–8] and the international normalised ratio (INR) (for VKAs)[9,10] due to inter-patient variability and/or food and drug interactions.

Instead, DOACs are administered in fixed dosages according to the indication, and there is generally no need to monitor levels.[1,2,11] Given the convenience and efficacy of DOACs, these agents have replaced the classical anticoagulants for many (but not all) indications.[11–13] Although there is no need to monitor the DOACs during anticoagulation therapy, there are several situations where measurement of plasma levels may be beneficial, for example prior to elective or emergency surgery to ensure absence of DOACs to prevent bleeding.[1–4,11] To measure DOACs, several laboratory methods have been developed.[1–4,11] Although liquid chromatography–mass spectrometry/mass spectrometry (LC–MS/MS) is sometimes touted as a gold standard, the complexity of the test, and the need for specialised instruments, prevents this method being used for urgent measurement of DOACs. Instead, modifications of standard laboratory hemostasis tests have become popular, with anti-Xa assays utilised for measuring anti-Xa DOAC agents, and the dilute thrombin time (dTT) or other direct thrombin inhibitor (DTI) assays used to measure dabigatran.[1–4,11] Most of these tests can be completed within 10 minutes on automated analyser platforms.[11]

Published reports of laboratory surveys of practice for these methods are scarce. For example, the RCPAQAP (Royal College of Pathologists of Australasia Quality Assurance Programs) reported findings with the locally available DOACs in 2015 (dabigatran)[14] and 2016 (apixaban and rivaroxaban).[15] There have been few other reports from external quality assessment (EQA) or proficiency testing from other groups.[16–20]

With this background in mind, we provide contemporary findings for DOAC testing in our geographic region, using recent data from the RCPAQAP. This is an international EQA program, currently with around 40–60 participants in each DOAC testing module. Contemporary data shows reasonable consistency in assays in current use, although a few assays predominate, and some changes have occurred over recent years. We hope our findings, reflecting on general consistency of test data related to DOAC testing helps reassure clinicians requesting DOAC level measurements, and helps support implementation of these assays in regions when commercially available options are mostly lacking (e.g., the USA).

2 | MATERIALS AND METHODS

2.1 | Setting

This study assesses data submitted by participants of the RCPAQAP in Haematology (https://rcpaqap.com.au/). It therefore represents 'real world' assessments of laboratories accredited to perform DOAC testing, although a variety of expertise might be expected. Supplementary Table 1 shows the current DOAC assays utilised by RCPAQAP participants. All DOAC measurements are reported to this program in ng/mL. As only dabigatran, rivaroxaban and apixaban are available for clinical use in our region, our data is restricted to these three DOACs. Supplementary Table 2 summarises the samples ($n = 20$ for each DOAC) that have been distributed to participants from 2019 to 2023 inclusive, representing the last 5 years of test data. Participants for the DOAC modules mostly derive from Australia, with additional representation from New Zealand, Hong Kong, Malaysia, South Africa, and Austria (Supplementary Table 3).

2.2 | Samples

DOAC samples (Supplementary Table 2) are now purchased by the RCPAQAP from Stago Diagnostics (Sydney, Australia) and comprise several different DOAC levels, with duplicate samples also sent in many years. Some DOAC level samples are targeted to be below or close to assay detection cut-off values of most manufacturers, and other levels targeted to be above the cut-off values of most manufacturers.

All samples are delivered to participants as lyophilised samples as 1.0 mL/vial. Four samples are sent per year as paired samples for two separate proficiency challenges, spaced out over a 12-month period. The samples are sent in semi-random fashion, and duplicates are sent over different surveys to help assess comparability or reproducibility between surveys (Supplementary Table 2).

2.3 | EQA program aims and strategy of sample dispatches

For DOAC testing, one major aim of the RCPAQAP is to provide laboratories with material that reflects a wide range of DOAC levels, from below cut-off values to above cut-off values. Another major aim is to assess and hopefully ensure testing precision and accuracy.

2.4 | Data analysis

Numerical values are submitted electronically by all participants for the tests they perform. This attempts to capture the normal test practice for each participant. Participants are also required to interpret their own test findings in terms of DOACs being 'detected' or 'not detected'; in some cases, participants report grades of DOAC

detection as 'low level', moderate level' or 'high level'. These participant interpretations are not formally assessed by the RCPAQAP, which instead only assesses numerical values for these modules. Although not formally assessed by the RCPAQAP, participant interpretations are periodically assessed and reported, as in the current report. Reported numerical values need to be within prescribed 'Analytical Performance Specifications' (APS), which are currently set as ±25.0 up to 100.0, ±25.0% for >100.0 ng/mL (i.e., the same APS for all three DOACs), for a participant result to be marked as 'within APS'. We note that these APS might be considered potentially wide, but seem reflective of current expected varied test practice. The target source for the APS is the calculated median of category (reagent) specific results.

2.5 | Ethics

As this is a review of EQA practice, not otherwise involving patients, specific Ethics approval for the study was not deemed to be required.

3 | RESULTS

3.1 | Evolution in test methodologies and participant numbers

Participation numbers have increased slightly over the years for anti-Xa DOACs (rivaroxaban, apixaban), but remained stable for dabigatran (Figure 1). The most utilised anti-Xa assay in each year was the Stago STA Liquid Xa, until recently exceeded by the HemosIL Xa, with lower numbers of Siemens Innovance Anti-Xa and Hyphen BIOPHEN DiXal/Heparin (LRT) reagents. In contrast, for dabigatran the Hyphen Hemoclot DTI assay was the clear favorite among participants, followed by HemosIL thrombin/DTI, and Stago thrombin and Siemens thrombin/Innovance DTI. It should be noted that this data reflects that which is self-reported by participants, and there were changes over time given emergence of manufacturer 'DTI' branded reagents replacing manufacturer branded thrombin. Given these transitions, it is also possible that some participants continued to report data as older methods whilst actually using the newer methods.

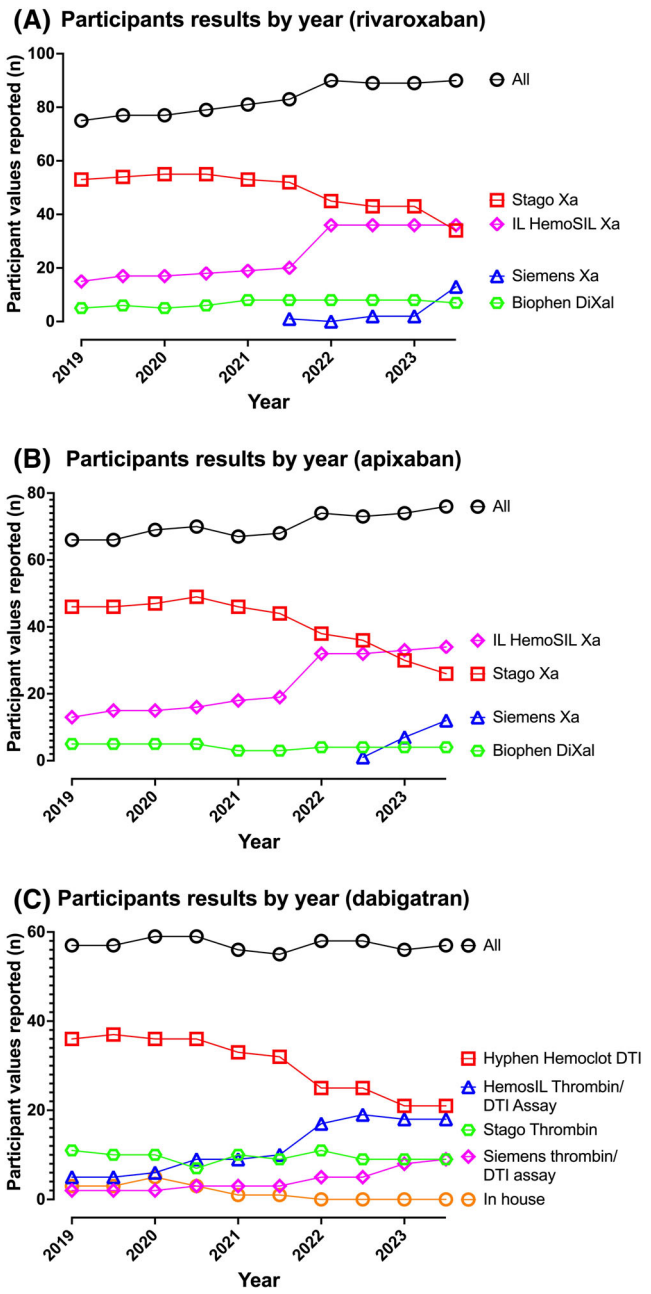

FIGURE 1 Participant submitted results for DOAC testing by year (2019–2023 inclusive). (A) rivaroxaban, (B) apixaban, and (C) dabigatran. Some participants report results for more than one instrument. Data shown for all methods and also individually for main methods in use. Data for Biophen DiXal also includes occasional use of Biophen Heparin (LRT) reagent.

3.2 | Intra-method and Inter-laboratory variability

Test data is shown for 2019 (Figure 2) and 2023 (Figure 3), representing the first and last years of data analysis, with data for other years shown in Supplementary Figures 1–3. Outlier data can occasionally be seen for all DOAC assays; these may reflect reporting variations, or random errors such as analytical issues, and transcription or computer data entry errors. The latter reflect typical but infrequent errors in laboratory reporting. Occasional transcription errors include when participants enter data for paired samples incorrectly swapped (examples in Figure 3 HA-RIV-23-03 vs. HA-RIV-23-04) or when incorrect units are entered (examples in Figure 3 HA-DAB-23-03 [where one participant entered 0.26 and 0.23 when values should be ~200] and HA-DAB-23-04 [0.07 and 0.05 entered when values should be ~50–70]). These outliers may reflect participants attempting to enter data in µg/mL. However, some outlier data is harder to explain, and may represent isolated technical issues on day of testing.

Although most methods yielded broadly similar values, some systematic differences can be noted. For example, Biophen users tended

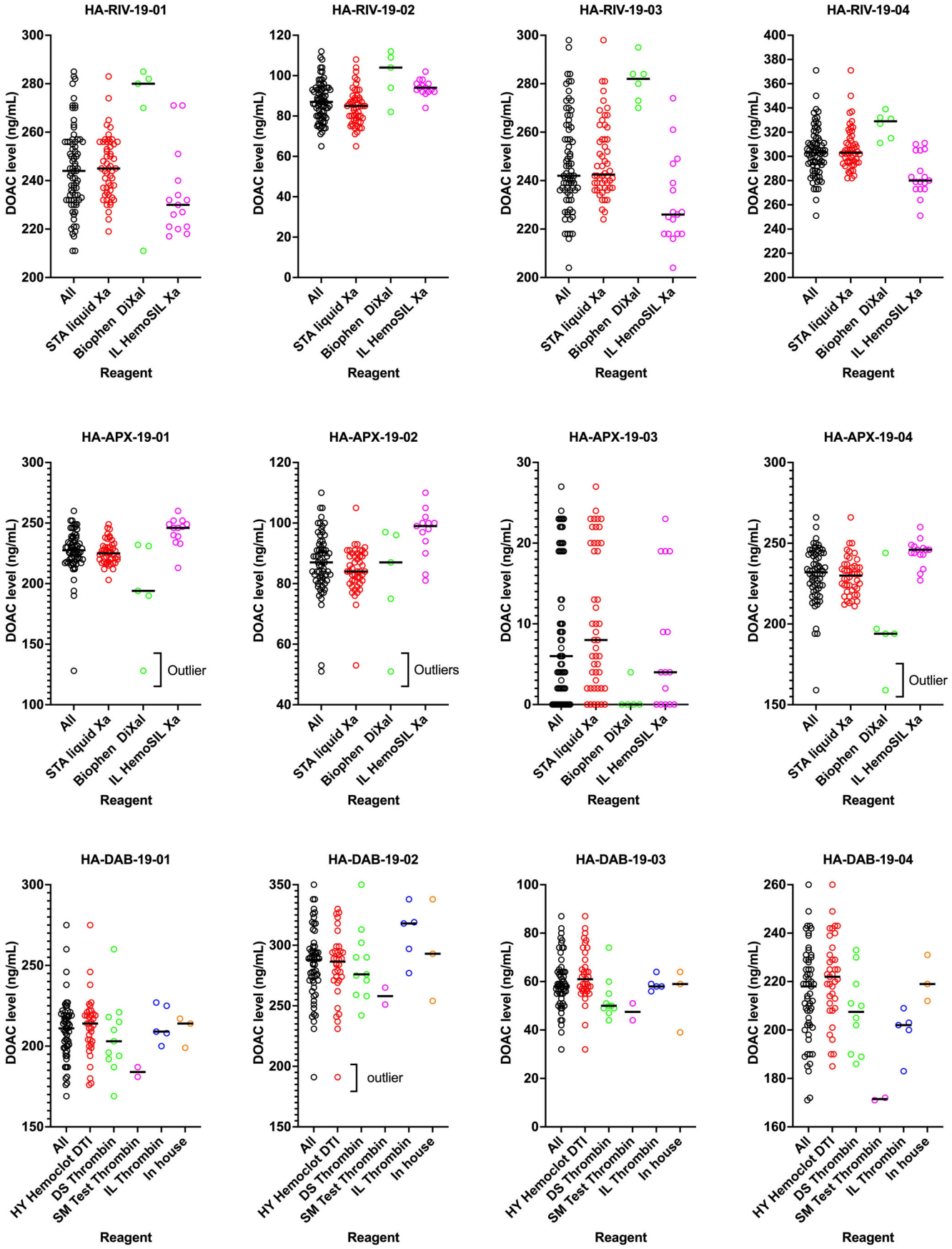

FIGURE 2 Summary reported values for direct oral anticoagulant samples tested in 2019. Data shown for all methods and also individually for main methods in use.

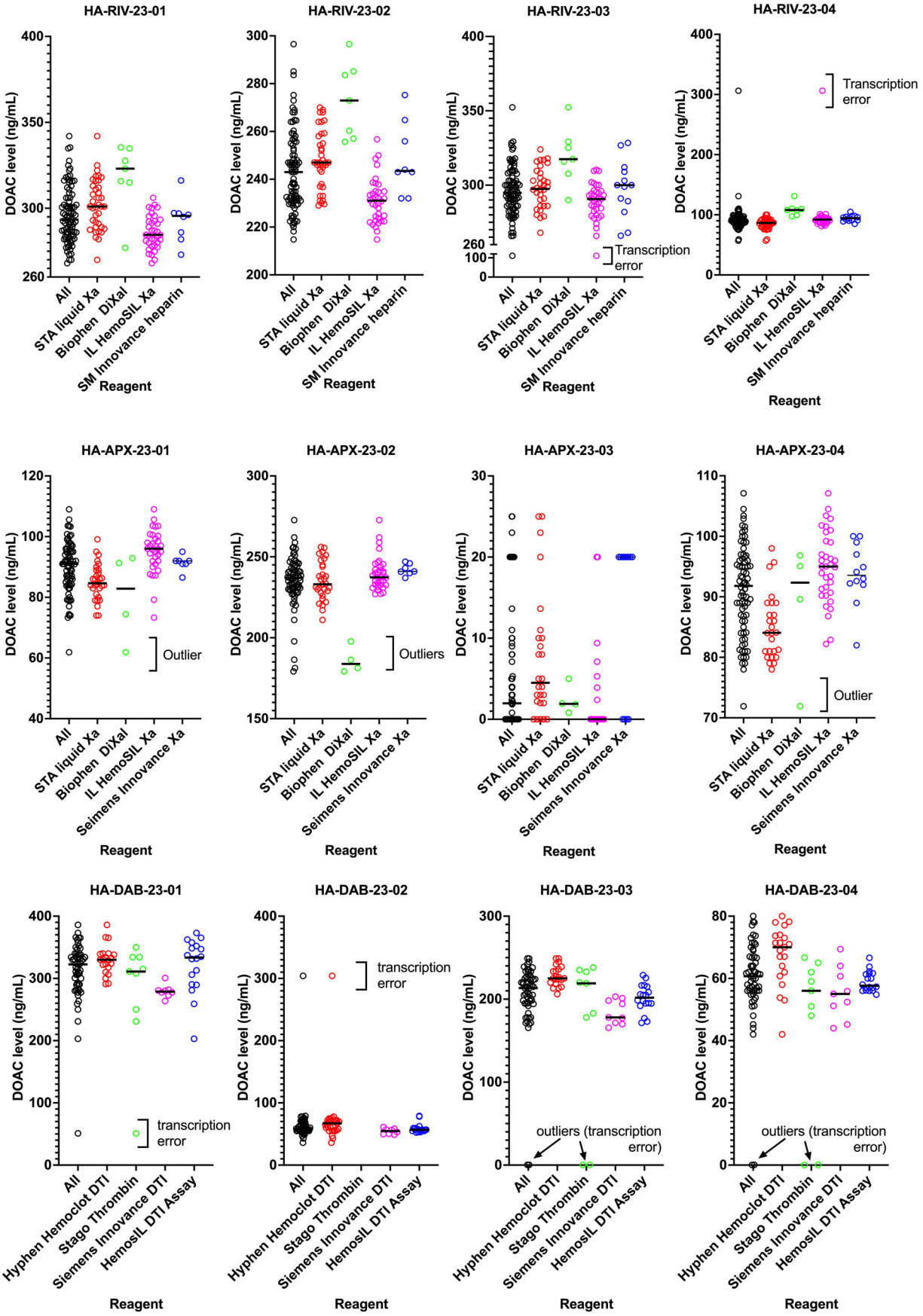

FIGURE 3 Summary reported values for direct oral anticoagulant samples tested in 2023. Data shown for all methods and also individually for main methods in use. The transcription error noted for dabigatran samples '03' and '04' were also submitted in incorrect numerical units.

to yield slightly higher values for rivaroxaban, and IL HemosIL users slightly lower values. For apixaban, the trend seemed reversed (lower with Biophen, higher with IL HemosIL). For dabigatran, users of Siemens reagents seemed to report slightly lower values than those using other reagents. However, in general, broadly similar ranges of DOAC levels were reported by participants to that targeted by the manufacturer (Supplementary Table 2).

Assay variability (identified as coefficient of variation [CV; %]) for each assessed sample and plotted against the overall mean reported value is shown in Figure 4. As might be expected, CVs increased as DOAC levels fell. Excluding the very high CVs seen with samples essentially not containing any DOACs, and caused by mathematical inclusion of very low numerators in the CV calculation, CVs tended to be <15% for rivaroxaban, <20% for apixaban and <25% for dabigatran (i.e., for samples containing DOACs). For samples containing >100 ng/mL DOAC, CVs tended to be <10% (rivaroxaban and apixaban) to <15% (dabigatran).

3.3 | Participant interpretations

In addition to providing numerical test data, RCPAQAP participants are required to provide an interpretation of whether the DOAC value obtained on the tested samples is above or below the assay cut-off value used in their laboratory—in other words, if DOAC is detected or not. These interpretations are not formally assessed by the RCPAQAP, but still provide an interesting analysis. Summary data representing the last 5 years of data is shown in Figure 5. Most participants correctly identified samples as either containing or not containing DOACs, although some participants reported 'detected' or 'low level' in samples without any apparent DOAC. Whilst there was some step-wise gradation in in participant reported DOAC levels versus 'grade' as low, moderate and high, there was substantial overlap across the categories, indicating different participant impressions regarding reported levels.

3.4 | Reproducibility of test results using repeat test samples

As noted, identical samples are sent to participants in different despatches (Supplementary Table 2). In general, numerical data returned by participants showed similar means and ranges for repeat sample testing (Figures 1, 2, and Supplementary Figures 1–3) and similar interpretations (Figure 5). This indicates good within laboratory or within method reproducibility, and acts as a surrogate marker of sample homogeneity.

4 | DISCUSSION

This contemporary assessment of DOAC testing practice from participants of the RCPAQAP provides an interesting evaluation of current

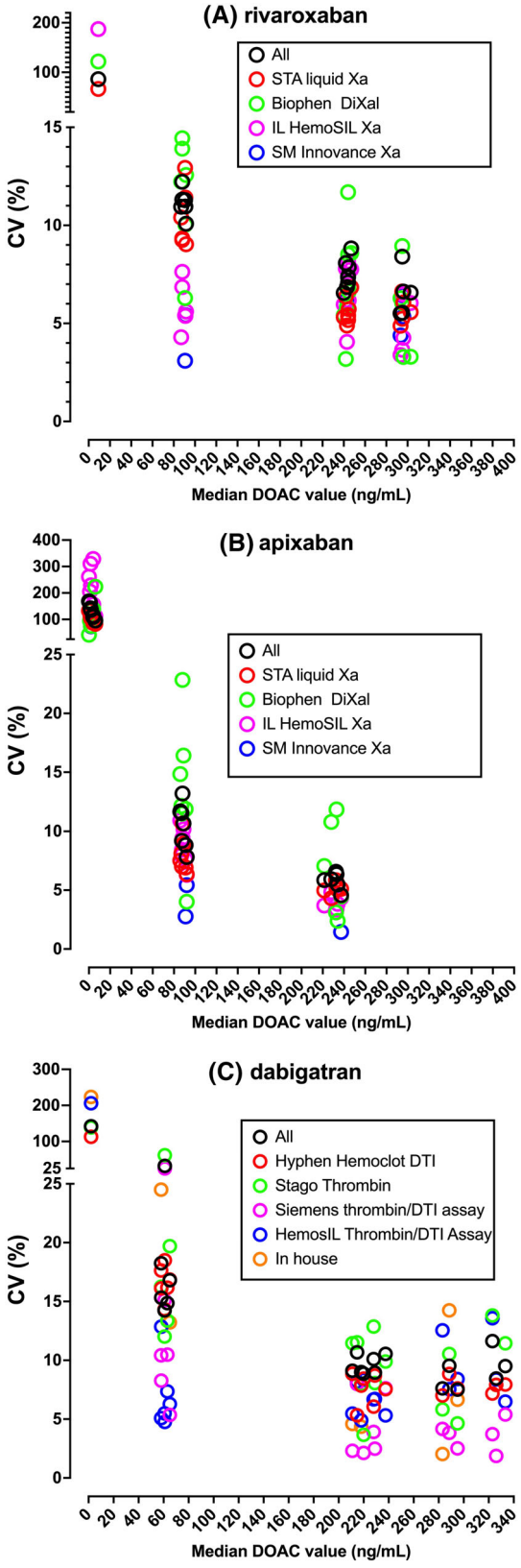

FIGURE 4 Coefficient of variation (CV) as percent for all reported test results (2019–2023 inclusive) for all data and for main methods in use, plotted against median direct oral anticoagulant level. (A) rivaroxaban, (B) apixaban, and (C) dabigatran.

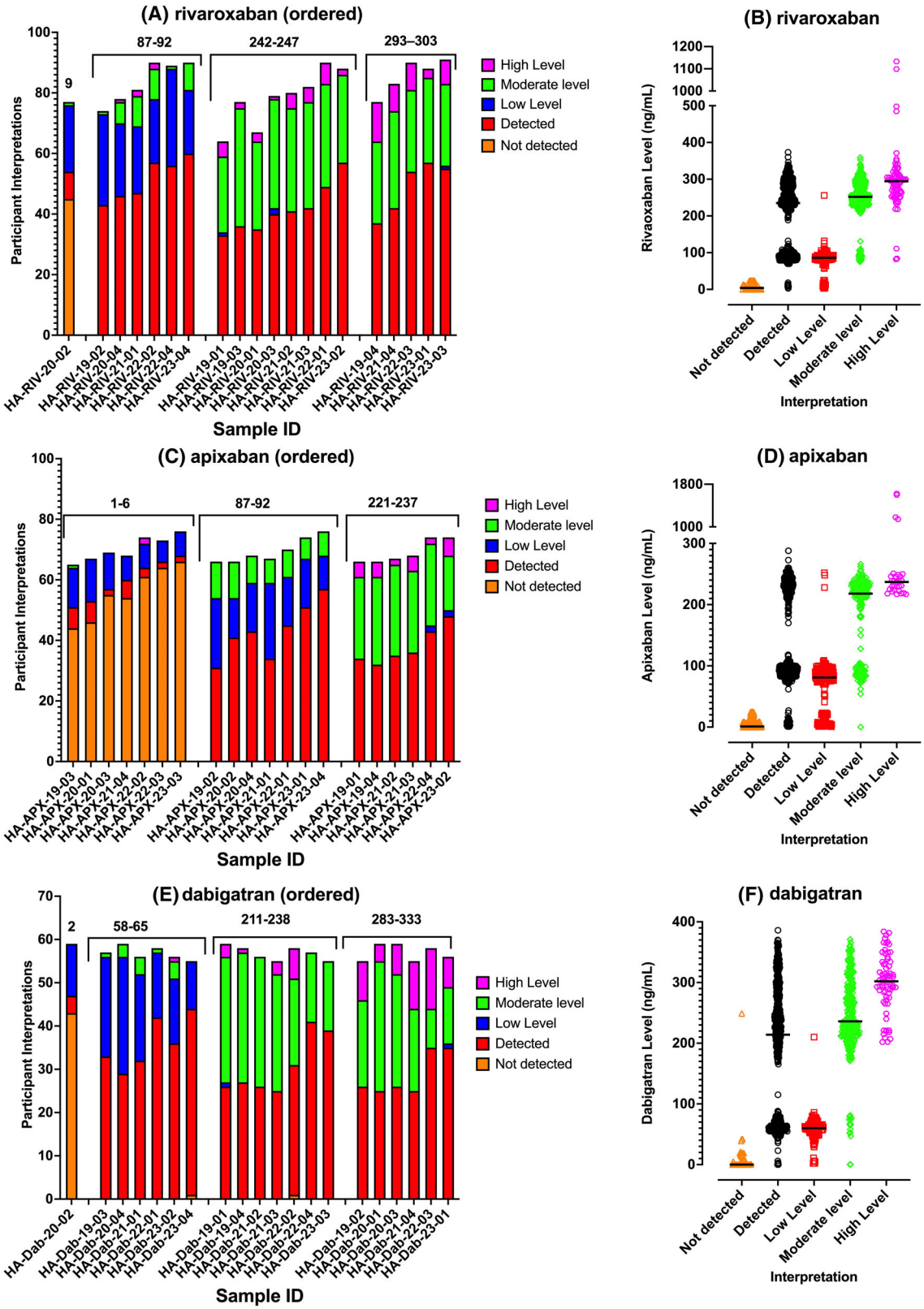

FIGURE 5 Participant interpretations for all tested direct oral anticoagulant (DOAC) samples from 2019 and 2023. (A) rivaroxaban, (C) apixaban and (E) dabigatran, are ordered into DOAC level groups, with median DOAC levels identified by numbers above the bars. (B) rivaroxaban, (D) apixaban and (F) dabigatran, show plots of participant interpretations against the participant reported DOAC level.

DOAC testing in 'real world' laboratories. This report is the first of this kind for the RCPAQAP, although earlier findings were reported during the formal establishment of the DOAC EQA programs.[14,15] The summarised contemporary data (last 5 years) is shown here for a large quantity of samples ($n = 20 \times 3$ DOACs), which have been cross-laboratory assessed in up to 90 instruments, depending on DOAC and data year (Figure 1).

4.1 | Literature review and comparison with other EQA findings

As part of this evaluation, we also performed a PubMed search, using the search string '(direct oral anticoagulants OR DOAC) AND ((external quality assessment) OR (external quality assurance) OR (proficiency testing))' (performed on 27th January, 2024). This search returned only 15 citations, which were then screened for relevance. Several citations were unrelated to DOAC EQA testing. From those relevant, Lindahl et al. reported on EQA data for dabigatran from Sweden.[16] This was a kind of exploratory study, looking at the effects of dabigatran on various coagulation tests, and similar to our earlier report in 2015.[14] Van Blerk et al. reported EQA data on apixaban from Belgium, again focussing on routine coagulation tests,[17] and this again comprises similar data to that we reported in 2016.[15] Studt et al. performed a multicentre study to evaluate the accuracy and consistency of anti-Xa activity measurement for determination of rivaroxaban plasma levels.[21] This was not an EQA study and simply reported on correlation or discrepancies in different anti-Xa assays against HPLC-MS. Tripodi et al. reported on interlaboratory variability in DOAC measurement, using EQA data from the Italian Federation of Thrombosis Centers,[18] with similar numbers of participants as reported here. They reported overall CVs of 8.7%, 8.4% or 10.3% for dabigatran, rivaroxaban and apixaban, respectively, somewhat similar to CVs identified in this study for samples containing >100 ng/mL of DOAC (Figure 4).

Smock and Moser, in a 2019 review of practice,[22] reported that in the USA, there were no Food and Drug Administration (FDA)-cleared assays for measuring DOACs (including dabigatran, rivaroxaban, apixaban, and edoxaban), and data from a 2015 NASCOLA survey indicated that approximately half of the special coagulation laboratories that participated did not offer tests for dabigatran, rivaroxaban, or apixaban. They also reported on the EQA data available at that time, and included discussion of other EQA reports, for example citing early ECAT/NASCOLA data showing CVs in the 11%–20% range for two specimens containing dabigatran and two containing rivaroxaban.[23] More recently, Hollestelle and Meijer presented EQA DOAC data over several years and demonstrated good correlation between tests and overall small interlaboratory variability (10% for dabigatran, rivaroxaban and apixaban and 12% for edoxaban).[19] They also reported greatest differences between various reagents for rivaroxaban, especially for concentrations below 100 ng/mL. Finally, Volod et al. reported on the interlaboratory performance in measurement of dabigatran and rivaroxaban, using data from CAP (College of American Pathologists) for the years 2013 to 2016.[20] They also reported similar CVs to ours, ranging from 11.6 to 17.2%, 9.3 to 12.3%, and 7.1 to 11.2% for dTT for 100, 200, and 400 ng/mL, dabigatran, respectively, and for anti-Xa assay ranging from 11.5% to 22.2%, 7.2% to 10.9%, and 6.4% to 8.1% for 50, 200, and 400-ng/mL targeted rivaroxaban drug concentrations, respectively.

In a 2022 publication,[11] it could be identified using 2021 data that numbers of participants for DOAC testing in various EQA programs differed strikingly. For example, 26, 28 and 51 participants were identified for dabigatran, apixaban and rivaroxaban respectively in the American College of Pathologists (CAP) program, compared to 1273 participants for LMWH, and over 4000 participants for APTT. In contrast, UKNEQAS (United Kingdom National External Quality Assessment Service) and ECAT (External quality Control of diagnostic Assays and Tests) had 66/98, 106/274 and 106/274 participants identified for dabigatran, apixaban and rivaroxaban respectively, compared to 383/394 for LMWH and 942/249 for APTT. The RCPAQAP had 56/66/83/127/777 listed for dabigatran, apixaban, rivaroxaban, LMWH and APTT, respectively. Thus, the CAP data is striking for relatively low DOAC testing compared to LMW/APTT and the RCPAQAP for relatively high DOAC testing compared to LMW/APTT.

A recent review of various FDA databases for 510 K,[24] premarket approval (PMA)[25] and de novo applications[26] could only identify one commercial anti-Xa assay (Werfen) currently approved for use for DOACs (apixaban and rivaroxaban), suggesting that many USA laboratories are likely using laboratory developed tests for assessing DOACs.

4.2 | Study limitations

There are various study limitations that we should highlight. First, samples are purchased for this EQA module and supplied by Stago Diagnostics. Essentially otherwise used as internal quality control material, these products do not reflect the same material as that of undiluted native patient plasma samples containing DOACs. Naturally, the RCPAQAP, like other EQA providers, must be pragmatic for EQA, since it is otherwise impossible to obtain the volumes of patient plasma required for EQA use, as otherwise would be needed, should undiluted patient plasma be used (e.g., for 100 instruments, with 1 mL despatches, as duplicate samples, with homogeneity and stability testing, would require >200 mL plasma, or a > 400 mL blood collection). This would need to be expanded $\times 2$ for 1 year of EQA for each DOAC. Nevertheless, evaluation of findings from EQA then needs to be tempered. Thus, although we can highlight that different reagents can lead to slightly differing numerical test results for DOAC level, the noted differences cannot be conclusively identified to be reflective of any expected patterns using real (undiluted) patient samples, since EQA samples have been 'contrived'. Moreover, we cannot identify any particular assay as being 'more accurate' than any other assay, or that reagent A is 'better' than reagent B for DOAC testing, since this material has not been assessed against any gold standard assay or material. We can only say that differences are observed in test results

from different reagents. Also, although we show differences according to test reagent, variation is most likely due to variation in the calibration plasma used to generate the calibration curve, and this data cannot be assessed by the RCPAQAP. Lastly, since data is collated as reported by participants, and sometimes errors are noted to occur, the reported variation in test values reflected by CVs are likely to be higher than those reflective of assay variation per se. The suitability of these commercial samples as being commutable to patient samples has not been formally assessed by the RCPAQAP, but is currently under consideration. A published report from NEQAS indicated commutability for plasma spiked with rivaroxaban.[27]

We also note that although samples not containing DOACS were used for the apixaban surveys, these were largely missing from surveys for rivaroxaban and dabigatran. This omission is unfortunate, and also marked for addressing in future surveys. The importance of assessing samples devoid of DOACs is important to identify low level detection limits for the DOACs, with such data utilised to identify safety of surgical intervention or need for reversal in bleeding. For example, Tomaselli et al. have published expert consensus guidance that bleeding patients with values >50 ng/mL and patients needing invasive procedures with values >30 ng/mL should be considered for reversal.[28]

5 | CONCLUSION

To our knowledge, we report the most comprehensive and contemporary evaluation of EQA findings related to DOAC measurement. Although we recognize limitations in the use of EQA to inform on DOAC testing, data generally identifies a positive trend, with broad similarity around reported DOAC levels across different methods (or perhaps using different calibrants), as well as generally acceptable inter-laboratory CVs (generally <15% for DOAC values >100 ng/mL). These findings are encouraging and should provide some reassurance to clinicians requesting these tests, as well as regulatory authorities considering approval of these tests for regions currently with limited regulatory-cleared tests (e.g., USA).

AUTHOR CONTRIBUTIONS

All authors contributed to either the study execution, study design, or data analysis. EJF wrote the original draft of the manuscript, which was then revised according to input from other contributors; all authors approved the manuscript for submission and publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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