Usual On-therapy Ranges of Drug Concentrations in Patients with Atrial Fibrillation Treated with Direct Oral Anticoagulants: A Systematic Review and Meta-analysis

Tim A.C. de Vries[1,2,3,4,*] Imaad U. Mallick[5,6,*] Vinai C. Bhagirath[6,7,8] John W. Eikelboom[6,7,8] Calvin Gomes[9] Qilong Yi[10] Sean McGrath[11] Jack Hirsh[7] Noel C. Chan[6,7,8]

[1] Department of Clinical and Experimental Cardiology and Cardiothoracic Surgery, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands
[2] Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, The Netherlands
[3] Department of Cardiology, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, The Netherlands
[4] Department of Cardiology, Rijnstate Hospital, Arnhem, The Netherlands
[5] School of Medicine, St. George's University, Grenada, West Indies
[6] Division of Hematology and Thromboembolism, Department of Medicine, Population Health Research Institute, Hamilton, Ontario, Canada
[7] Division of Hematology and Thromboembolism, Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[8] Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
[9] School of Medicine, Poznan University of Medical Sciences, Poznan, Poland
[10] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada
[11] Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

Address for correspondence Tim A.C. de Vries, MD, MSc, Department of Clinical and Experimental Cardiology and Cardiothoracic Surgery, Amsterdam UMC, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (e-mail: T.A.deVries@AmsterdamUMC.nl).

Thromb Haemost

Abstract

Background Although most patients with atrial fibrillation (AF) receiving a direct oral anticoagulant (DOAC) do not require drug concentration measurements, there are situations where such information could be useful. Existing guidance documents provide usual on-therapy ranges for drug concentrations, but these have important limitations.

Methods This is a systematic review and meta-analysis of studies reporting trough and peak levels of DOAC regimens approved for stroke prevention in AF. We used random effects models and the quantile estimation method to estimate the median and a usual on-therapy range (10^{th} and 90^{th} percentiles).

Results Of 4,822 unique publications, 53 studies met eligibility (29,266 trough and 12,103 peak levels). Usual on-therapy ranges for trough levels were 38 to 155 and 58 to 206 ng/mL for apixaban 2.5 and 5 mg twice daily; 35 to 138 and 33 to 151 ng/mL for dabigatran 110 and 150 mg twice daily; 8 to 54 and 13 to 66 ng/mL for edoxaban 30 and 60 mg daily; and 16 to 74 and 19 to 72 ng/mL for rivaroxaban 15 and 20 mg daily. The corresponding range for peak levels were 96 to 251 and 132 to 343; 65 to 223 and 76 to 285; 57 to 219 and 127 to 407; 131 to 384, and 169 to 313 ng/mL, respectively.

Conclusion This systematic review and meta-analysis provides updated and more representative usual on-therapy ranges of DOAC levels in patients with AF.

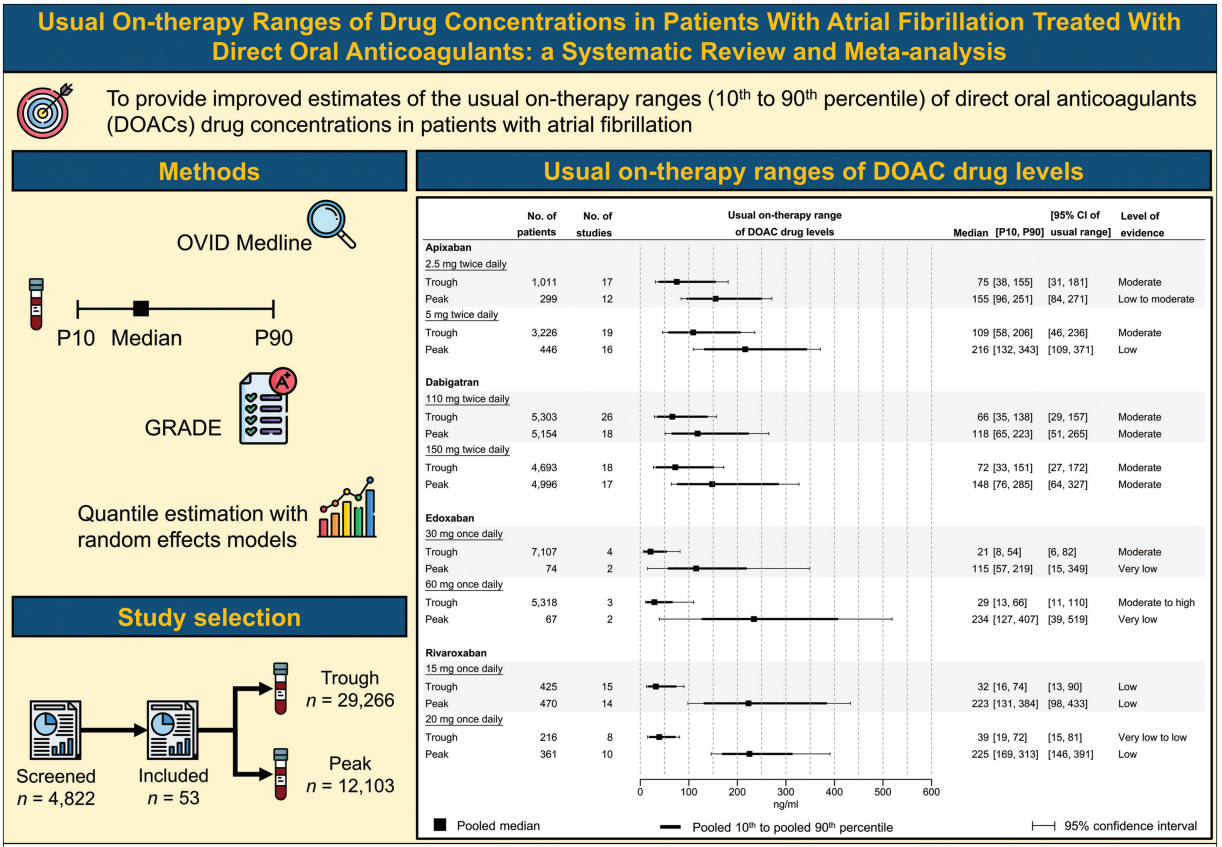
Keywords
- direct oral anticoagulant
- blood coagulation tests
- drug monitoring
- biological variation
- population
- factor Xa inhibitors
- anticoagulants
- hemorrhage

* *These authors serve as Co-first authors.*

received
March 16, 2024
accepted after revision
October 12, 2024

DOI https://doi.org/10.1055/a-2446-1348.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Visual summary. Usual on-therapy ranges of drug concentrations in patients with atrial fibrillation treated with direct oral anticoagulants. CI confidence interval; DOAC direct oral anticoagulant; GRADE Grading of Recommendations Assessment, Development and Evaluation; P10 10th percentile; P90 90th percentile.

Introduction

Anticoagulant therapy has been revolutionized by the replacement of drugs requiring dose adjustments based on results of coagulation assays (heparin and vitamin K antagonists), with anticoagulants that do not require laboratory monitoring.[1] The shift, which began in the 1990s with the introduction of low molecular weight heparin, improved the convenience of anticoagulant therapy, and reduced cost by minimizing the need for in-hospital treatment.[1] The introduction of direct oral anticoagulants (DOACs) has further simplified anticoagulation therapy. All four available DOACs (i.e., apixaban, dabigatran, edoxaban, and rivaroxaban), when used in fixed doses without laboratory monitoring of anticoagulant activity, are at least as effective and safe as warfarin for the prevention of ischemic strokes in patients with nonvalvular atrial fibrillation (AF).[1–4] As a result, DOACs are used in fixed doses, either in a high dose or low dose depending on the patient's characteristics.[1–3]

Although most patients treated with fixed doses of DOACs do not need laboratory monitoring, there are clinical circumstances in which measurements of drug level might be desirable.[1,5,6] In the absence of therapeutic ranges, less reliable metrics such as usual on-therapy ranges (10th to 90th or 5th to 95th percentile ranges) of trough and peak drug concentrations have been proposed to guide physicians if they consider it necessary to measure drug levels.[3,5] The previously published usual on-therapy ranges were derived from few studies of limited applicability to patients with AF (e.g., derived from healthy subjects, patients with other indications for treatment with a DOAC, or reduced validity due to reliance on pharmacokinetic modelling.[3,5] Since the initial publication of the guidance documents and product monographs, over 50 clinical studies have been published examining drug levels in patients taking DOACs for stroke prevention in AF.[6–58]

In this systematic review and meta-analysis, we provide updated estimates for the 10th to 90th percentile ranges (i.e., middle 80% of drug levels) for trough and peak concentrations of the four approved DOACs when used in patients with AF using assays commonly used in clinical practice. This update provides clinicians with more representative estimates of the usual on-therapy ranges of DOACs than previously reported, to help guide their decision-making.

Methods

Protocol

This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (PRISMA checklist provided in ►**Supplementary Table S1** of **Supporting Information File 1**, available in online version only).[59] Our protocol is provided in **Supporting Information File 2** (available in online version only).

Data Sources and Searches

We electronically searched MEDLINE via Ovid for articles reporting on plasma concentrations of DOACs in patients with AF treated with DOACs to prevent ischemic strokes published between the inception of the database and January 2023. The full search strategy is presented in ►**Supplementary Table S2** of **Supporting Information File 1** (available in online version only). This search was supplemented by manual review of the reference list of articles identified from the initial search.

Study Selection

Studies were eligible for inclusion if they reported either or both trough and peak drug levels in ng/mL (or in units that allowed for direct conversion to ng/mL) for DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) approved for stroke prevention in AF. If there was overlap in study populations among primary studies, we avoided double counting by using the data of interest from the more comprehensive publication.

Eligible studies included randomized controlled trials and observational studies that collected blood samples and reported cross-sectional data on drug levels. We excluded case reports and case series, pharmacokinetic simulations, studies that did not separately report DOAC drug levels of patients with AF from those who were treated for other indications (e.g., treatment or prevention of venous thromboembolism), as well as reports that did not differentiate levels by DOAC type and administered dose. We further excluded studies written in a non-English language and those with total sample size of <10 patients. After deduplication, all hits were screened for eligibility by two reviewers (I.U.M. and C.G.). In the instance of disagreement, the final decision was determined by a third reviewer (T.A.C.dV. or N.C.C.).

Data Extraction and Estimation of Nonreported Percentiles of Drug Concentrations

Two reviewers (I.U.M. and C.G.) independently extracted data using a standardized case report form that included the following variables: the number of patients, the DOAC dose and frequency, measures of distribution (mean, median, standard deviation, percentiles, interquartile range) of trough and peak DOAC drug concentrations for each DOAC regimen, and the laboratory method used to determine levels. The percentiles of interest were the 50th, 10th, and 90th percentiles. If not reported in the individual studies, these percentiles were calculated directly from the original dataset if the study was published by the authors of the current review,[6,15,42] or in most situations, these were estimated using simulations based on the published measures of central tendency and dispersion. More details regarding these simulation strategies are described in **Supporting Information File 2** (available in online version only).

Outcome Measures

The outcomes of interest were the 50th (median), 10th, and 90th percentile drug concentration for each DOAC regimen at trough and at peak. We defined the usual on-therapy range as the range spanning between the pooled 10th and 90th percentiles of drug level. We also report the lower bound of the 95% confidence interval (CI) of the pooled 10th percentile value and the upper bound of the 95% CI of the pooled 90th percentile value to provide a more conservative estimate of the usual on-therapy range.

Statistical Analyses

We estimated the pooled median, 10th and 90th percentile of DOAC drug concentration in ng/mL for each respective dose using the quantile estimation (QE) method.[60,61] This method estimates the variance of the study-specific medians from the reported summary statistics and then performs an inverse–variance weighted meta-analysis of medians.[60,61] We applied the same estimation strategy to estimate the pooled 10th and the pooled 90th percentile of trough and peak levels for each DOAC dosing regimen.

In all models, we prioritized summary statistics reported in the primary studies over simulated ones. Because the distributions of DOAC drug levels are right-skewed, we did not use the reported mean and standard deviation of some studies because the QE method would assume that data were normally distributed. Instead, for these studies, we used the simulated median, 25th and 75th percentile values. Given the method of data collection and the likely heterogeneity between studies due to differences in populations and methods of measurement, we used the random effects model (REM) in all analyses.[62] More details on the performed statistical analyses are provided in **Supporting Information File 2** (available in online version only).

Sensitivity Analyses

To assess the robustness of our findings on 10th and 90th percentile values, we performed two sets of prespecified sensitivity analyses for DOAC dosing regimen and one post hoc defined analysis. As defined in our protocol, we only considered these analyses whenever at least 10 studies provided data on the percentile of interest (**Supporting Information File 2**, available in online version only).[63]

In these analyses we redetermined the on-therapy ranges (i.e., 10th and 90th percentiles) selecting only the studies (1) at low risk of bias and low concern of inapplicability to our review question, (2) for which the 10th and 90th percentile values were provided in the report, and (3) that determined levels with liquid chromatography–mass spectrometry/mass spectrometry.

We used mixed-effects models to assess for significant differences between the subsets of studies using the

dichotomized variable as a potential modifier (i.e., low risk of bias and low concern of inapplicability vs. other studies, reported vs. simulated percentile of interest, or liquid chromatography–mass spectrometry/mass spectrometry vs. chromogenic assays). We kept Tau constant if there were five or fewer studies in either subset[63] and defined a significant difference between the subsets as a Wald test producing a two-tailed p-value < 0.05.

Quality Assessments

Assessing the quality of evidence of systematic reviews reporting on usual on-therapy ranges is less well established. We adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the quality of evidence for each outcome (i.e., median, 10th percentile, 90th percentile) of each DOAC dosing regimen.[64] To rate each study on their risk of bias and our concern of indirectness, we answered several prespecified signaling questions. These signaling questions sought to assess the risk of bias due to patient selection (domain 1 of QUADAS-2 tool) and due to method of drug concentration measurement (domain 2 through 4 of QUADAS-2 tool), as well as our concern of indirectness due to patient selection (►**Supplementary Tables S1**–**S4** in **Supporting Information File 3**, available in online version only).[65] The considerations and criteria for performing the quality assessments and rating of each domain (i.e., risk of bias, indirectness, inconsistency, and precision), including our rationale to not perform a formal publication bias assessment, are presented in ►**Supplementary Table S5** of **Supporting Information File 3** (available in online version only). The interpretation of the level of evidence ratings are described in ►**Supplementary Table S6** of **Supporting Information File 3** (available in online version only).

Results

Study Selection

We identified 4,833 publications of which 11 were duplicates. We screened the title and abstract of the 4,822 unique hits, of which 4,460 were excluded because they were irrelevant to our review question. After reading the full text, we excluded another 309 from the remaining 362 hits and were left with a total of 53 studies (►**Fig. 1**).[6–58] These included studies collectively reported on a total of 29,266 trough levels and 12,103 of peak levels. The characteristics of the included studies are presented in ►**Supplementary Table S1** of **Supporting Information File 4** (available in online version only).

Usual On-Therapy Ranges

In this section we present the usual on-therapy ranges of trough and peak levels of DOAC doses approved in most regulatory regions. A more detailed description of the results of each meta-analytic model is provided in **Supporting Information File 4** (available in online version only), which includes the number of studies and patients available, measures of heterogeneity, as well as the ranges of the less commonly used dosing regimens.

Apixaban: ►**Fig. 2** illustrates the usual on-therapy ranges of both trough and peak concentrations for the two approved dosing regimens of apixaban.

For the 2.5 mg twice daily dose of apixaban, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 38 to 155 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles of 31 and 181 ng/mL, respectively. The corresponding range for peak levels is 96 to 251 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles of 84 and 271 ng/mL, respectively.

For the 5 mg twice daily dose of apixaban, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 58 to 206 ng/mL, with lower and upper bounds of the 95% CI for 10th and 90th percentiles, respectively, of 46 and 236 ng/mL. The corresponding range for peak levels is 132 to 343 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 109 and 371 ng/mL.

Dabigatran: ►**Fig. 3** illustrates the usual on-therapy ranges of both trough and peak concentrations for the two commonly approved dosing regimens of dabigatran (i.e., 110 mg twice daily and 150 mg twice daily). The usual on-therapy ranges of all three available dabigatran dosing regimens, which includes the 75 mg twice daily dose, are presented in ►**Fig S2** of **Supporting Information File 4** (available in online version only).

For the 110 mg twice daily dose of dabigatran, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 35 to 138 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 29 and 157 ng/mL. The corresponding range for peak levels is 65 to 223 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 51 and 265 ng/mL.

For the 150 mg twice daily dose of dabigatran, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 33 to 151 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 27 and 172 ng/mL. The corresponding range for peak levels is 76 to 285 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 64 and 327 ng/mL.

Edoxaban: ►**Fig. 4** illustrates the usual on-therapy ranges of both trough and peak concentrations for the two commonly approved dosing regimens of edoxaban (i.e., 30 mg once daily and 60 mg once daily). The usual on-therapy ranges of all three available edoxaban dosing regimens, which includes the 15 mg once daily dose, are presented in ►**Fig S3** of **Supporting Information File 4** (available in online version only).

For the 30 mg once daily dose of edoxaban, the pooled estimate for the usual on-therapy range (10th to 90th

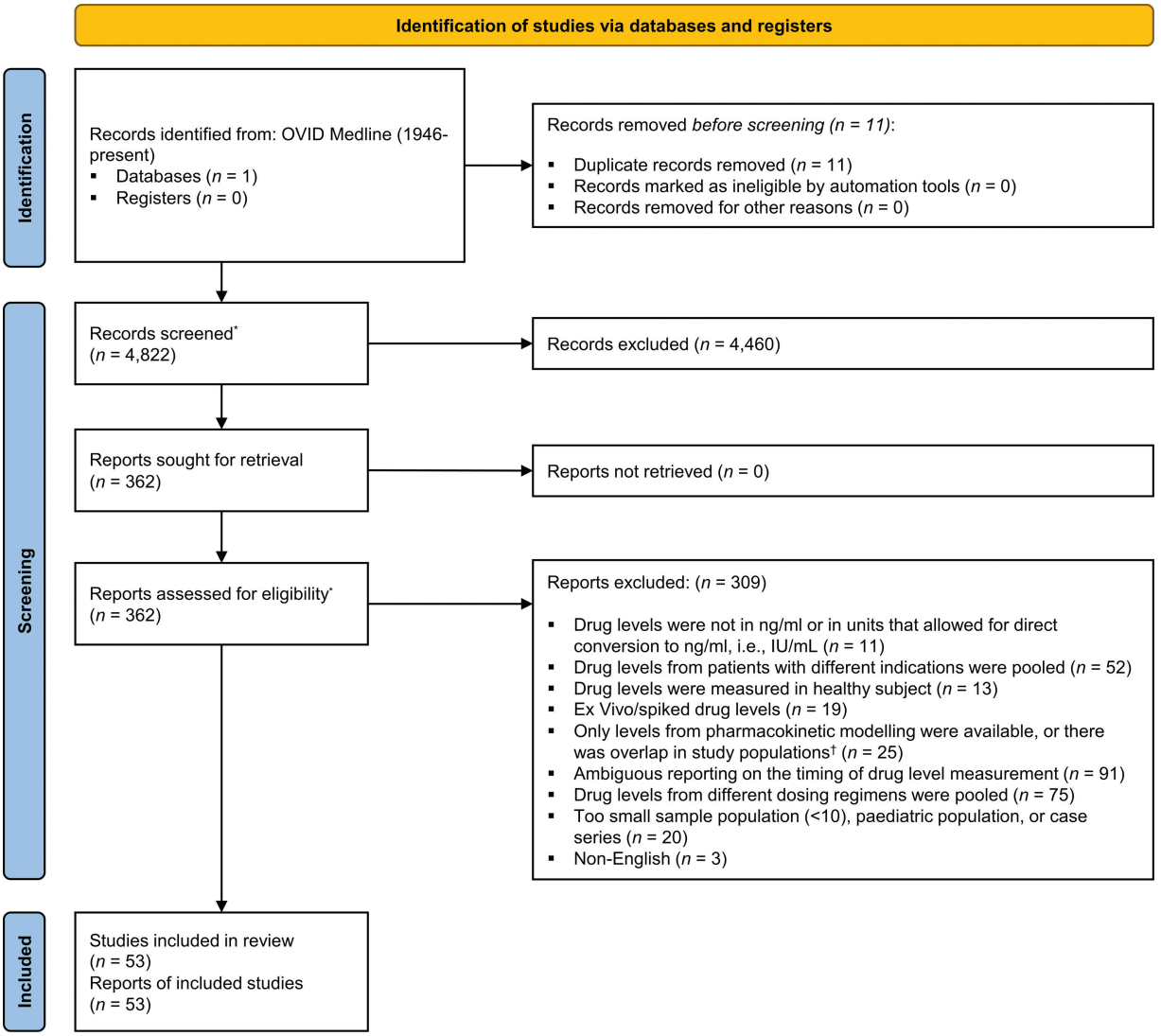


Fig. 1. Flow of study selection. This flow diagram illustrates the flow of study selection. * After deduplication, all hits were screened for eligibility by two reviewers (I.U.M. and C.G.). In the instance of disagreement, the final decision was determined by a third reviewer (T.A.C.dV. or N.C.C.); † If there was overlap in study populations among primary studies, we avoided double counting by using the data of interest from the more comprehensive publication.

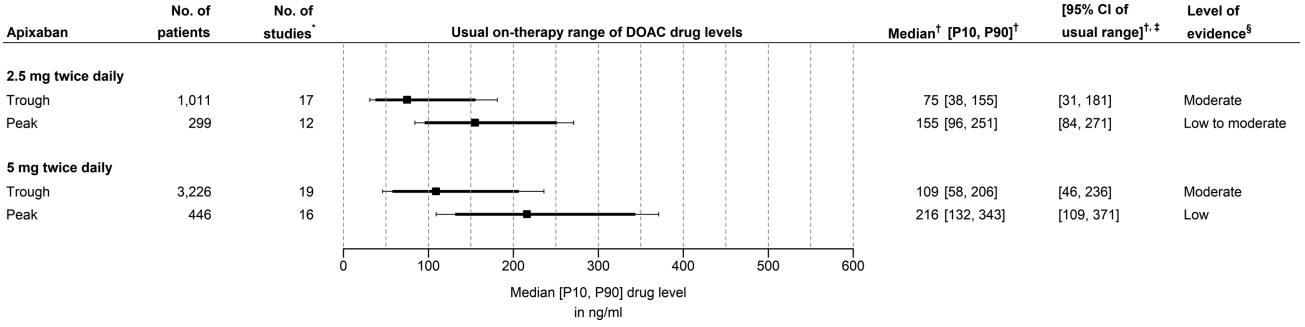


Fig. 2 Median (and 10th–90th percentiles) of drug levels for apixaban. The squares represent the pooled median values, the solid bold lines the pooled estimates for the 10th to 90th percentile range, and the whiskers the interval from the lower bound of the 95% CI of the pooled 10th percentile (left side) to the upper bound of the 95% CI of the pooled 90th percentile value (right side). P10 10th percentile; P90 90th percentile; CI, confidence interval; DOAC, direct oral anticoagulant; No., number. *Some studies reported on multiple subgroups of patients. Each subgroup was then considered a unique study; †Estimated with random effects models using the (modified) QE method;[60,61] ‡the interval from the lower bound of the 95% CI of the pooled 10th percentile to the upper bound of the 95% CI of the pooled 90th percentile value; §Level of evidence following the GRADE-framework and determined for each outcome of interest (i.e., median, 10th percentile, and 90th percentiles).[64]

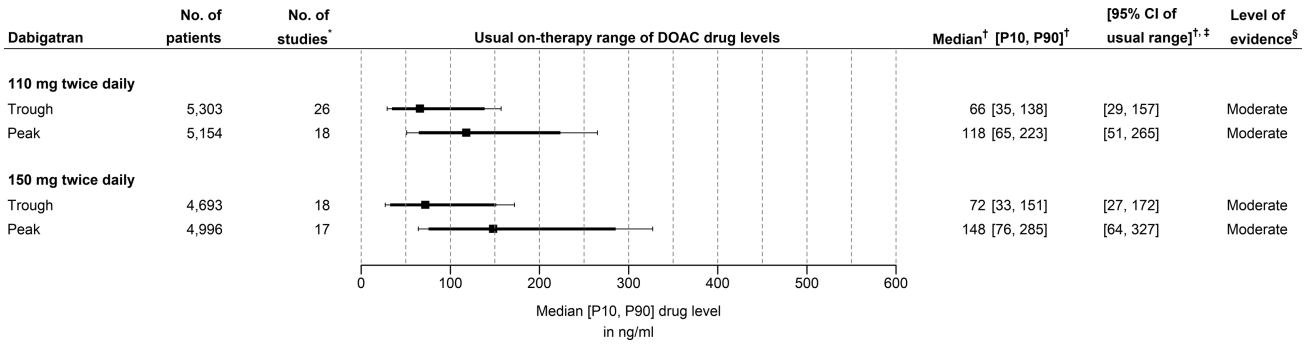


Fig. 3 Median (and 10th–90th percentiles) of drug levels for dabigatran. The usual on-therapy ranges of the 75 mg twice daily dose are presented in ►**Supplementary Fig. S2** of **Supporting Information File 4** [available in online version only]. The squares represent the pooled median values, the solid bold lines the pooled estimates for the 10th to 90th percentile range, and the whiskers the interval from the lower bound of the 95% CI of the pooled 10th percentile (left side) to the upper bound of the 95% CI of the pooled 90th percentile value (right side). P10 10th percentile; P90 90th percentile; CI confidence interval; DOAC direct oral anticoagulant; No. number. *Some studies reported on multiple subgroups of patients. Each subgroup was then considered a unique study; †Estimated with random effects models using the (modified) QE-method;[60,61] ‡the interval from the lower bound of the 95% CI of the pooled 10th percentile to the upper bound of the 95% CI of the pooled 90th percentile value; §Level of evidence following the GRADE-framework and determined for each outcome of interest (i.e., median, 10th percentile, and 90th percentile).[64]

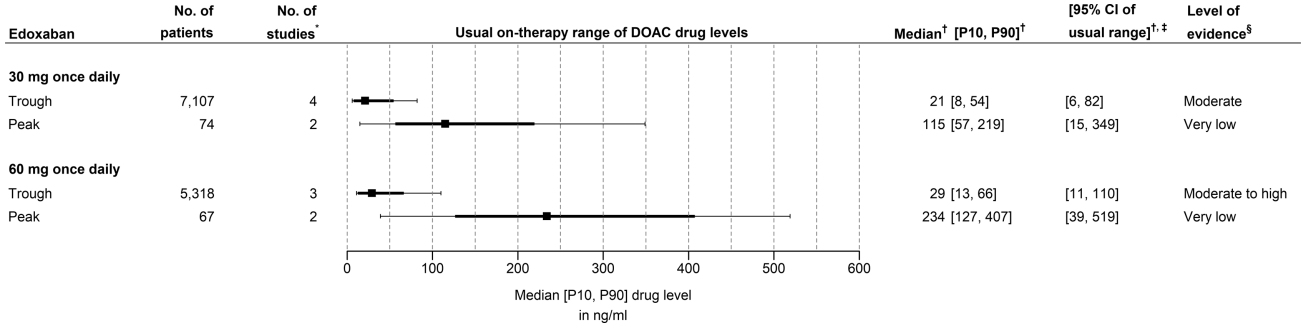


Fig. 4 Median (and 10th–90th percentiles) of drug levels for edoxaban. The usual on-therapy ranges of the 15 mg once daily dose are presented in ►**Supplementary Fig. S3** of **Supporting Information File 4** [available in online version only]. The squares represent the pooled median values, the solid bold lines the pooled estimates for the 10th to 90th percentile range, and the whiskers the interval from the lower bound of the 95% CI of the pooled 10th percentile (left side) to the upper bound of the 95% CI of the pooled 90th percentile value (right side). *P10* 10th percentile; *P90* 90th percentile; *CI* confidence interval; *DOAC* direct oral anticoagulant; *No.* number. * some studies reported on multiple subgroups of patients. Each subgroup was then considered a unique study; † estimated with random effects models using the (modified) QE-method;[60,61] ‡ the interval from the lower bound of the 95% CI of the pooled 10th percentile to the upper bound of the 95% CI of the pooled 90th percentile value; § Level of evidence following the GRADE-framework and determined for each outcome of interest (i.e., median, 10th percentile, and 90th percentile).[64]

percentile range) of trough levels is 8 to 54 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 6 and 82 ng/mL. The corresponding range for peak levels is 57 to 219 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 15 and 349 ng/mL.

For the 60 mg once daily dose of edoxaban, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 13 to 66 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 11 and 110 ng/mL. The corresponding range for peak levels is 127 to 407 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 39 and 519 ng/mL.

Rivaroxaban: ►**Fig. 5** illustrates the usual on-therapy ranges of both trough and peak concentrations for the two commonly approved dosing regimens of rivaroxaban (i.e., 15 mg once daily and 20 mg once daily). The usual on-therapy ranges of all three available rivaroxaban dosing regimens, which includes the 10 mg once daily dose, are presented in ►**Fig. S4** of **Supporting Information File 4** (available in online version only).

For the 15 mg once daily dose of rivaroxaban, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 16 to 74 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 13 and 90 ng/mL. The corresponding range for peak levels is 131 to 384 ng/mL, with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 98 and 433 ng/mL.

For the 20 mg once daily dose of rivaroxaban, the pooled estimate for the usual on-therapy range (10th to 90th percentile range) of trough levels is 19 to 72 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles,

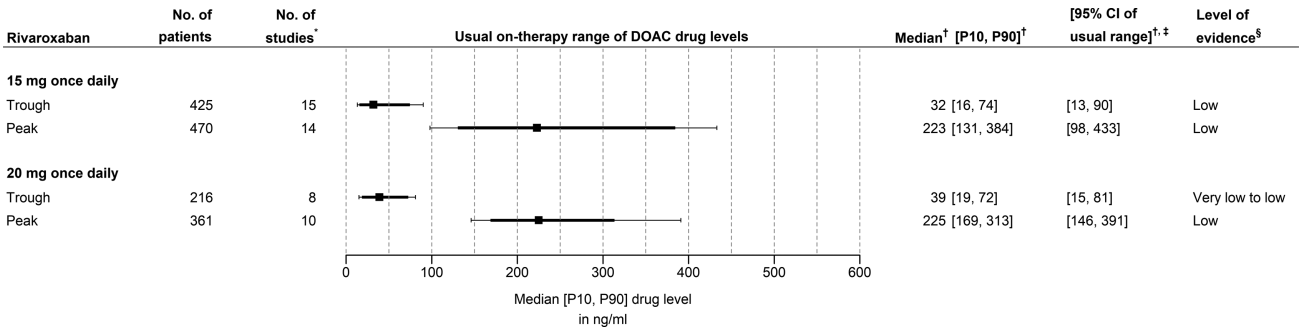


Fig. 5. Median (and 10th – 90th percentiles) of drug levels for rivaroxaban. The usual on-therapy ranges of the 10 mg once daily dose are presented in ►**Supplementary Fig. S4** of **Supporting Information File 4**. The squares represent the pooled median values, the solid bold lines the pooled estimates for the 10th to 90th percentile range, and the whiskers the interval from the lower bound of the 95% CI of the pooled 10th percentile (left side) to the upper bound of the 95% CI of the pooled 90th percentile value (right side). *P10* 10th percentile; *P90* 90th percentile; *CI* confidence interval; *DOAC* direct oral anticoagulant; *No.* number. * some studies reported on multiple subgroups of patients. Each subgroup was then considered a unique study; † estimated with random effects models using the (modified) QE-method;[60,61] ‡ the interval from the lower bound of the 95% CI of the pooled 10th percentile to the upper bound of the 95% CI of the pooled 90th percentile value; § Level of evidence following the GRADE-framework and determined for each outcome of interest (i.e., median, 10th percentile, and 90th percentile).[64]

respectively, of 15 and 81 ng/mL. The corresponding range for peak levels is 169 to 313 ng/mL with lower and upper bounds of the 95% CIs for 10th and 90th percentiles, respectively, of 146 and 391 ng/mL.

The level of evidence for all outcomes (i.e., median, 10th percentile, 90th percentile) of each DOAC dosing regimen ranged from high to very low as reported in ►**Supplementary Table S12** of **Supporting Information File 3** (available in online version only). The level of evidence was based on our assessments of the risk of bias, indirectness, inconsistency, and imprecision assessments (summarized in ►**Supplementary Tables S7**–**S11** of **Supporting Information File 3**, available in online version only).

Sensitivity Analyses

Performing the sensitivity analysis was impossible (because only a single study was available or all studies fell into the same category) or noninformative because fewer than 10 studies were available in 30 (68%) of analyses on risk of bias and concern of inapplicability, 22 (50%) on method of data extraction, and 22 (50%) on the laboratory methods used to determine levels.

For the DOAC regimens for which these analyses were feasible, rather than including all eligible studies, selecting only the studies at low risk of bias and concern of inapplicability studies (►**Supplementary Table S1** [available in online version only] and ►**Supplementary Figs. S1**–**S4** of **Supporting Information File 5** [available in online version only]), those studies that provided the 10th and 90th percentile values in their report (►**Supplementary Table S2** and ►**Figs. S5**–**S8** of **Supporting Information File 5** [available in online version only]), or studies that used liquid chromatography–mass spectrometry/mass spectrometry to determine levels (►**Supplementary Table S3** and ►**Supplementary Figs. S9**–**S12** of **Supporting Information File 5** [available in online version only]) did not result in consistently higher or lower 10th or 90th percentile values.

Discussion

In this systematic review and meta-analysis, we provide clinicians with the best-available information on the usual on-therapy range of drug levels in patients taking DOACs for stroke prevention in nonvalvular AF. We pooled data from 53 studies reporting on a total of 29,266 trough levels and 12,103 peak levels to generate estimates of the usual on-therapy range for trough or peak levels for approved dosing regimens of four DOACs.[6–58] Our estimates overlap those reported in guidelines and monographs[3,5] but are more representative because these were derived from a more comprehensive dataset that included only patients with AF and excluded pharmacokinetic modelling studies. Despite the methodological limitations of our study and of those of the included studies, our usual on-therapy ranges are an improvement on those currently reported. Our estimates better reflect trough and peak levels of all approved dosing regimens in AF, because we took indication and timing of sample collection into consideration.

These usual on-therapy ranges for trough and peak levels of DOACs can help clinicians who decide to measure levels to manage their patients who experience unexpected bleeding as well as those who were ineligible for inclusion or were underrepresented in the randomized trials. About 25% of patients treated in clinics who are prescribed the lower dose of a DOAC do not meet the recommended dose reduction criteria (i.e., off-label dose reduction).[66,67] Clinicians who use off-label dosing mainly select the lower dose and use this dose in patients who they suspect are at high risk of bleeding or drug overexposure. For example, patients with severe comorbidities

(e.g., advanced kidney or liver disease), those with extreme clinical characteristics (e.g., extremes of body weight or age), and patients who are taking drugs that are known to interact with a DOAC.[3,5] In such patients, the risk of underdosing could be mitigated if the dose reduction is limited to patients with consistently high drug levels.[6,42] Although the use of off-label dose adjustment in selected patients is debated,[3,66–68] there is evidence that drug levels are associated with thromboembolic and bleeding events,[10,34,36,69–71] and that use of the dosages currently approved for patients with AF is likely to result in unacceptably high bleeding risks in selected patients.[72,73]

Strengths and Limitations

The main strengths are the comprehensive search with inclusion of more than 50 studies of patients with AF from across the globe. As a result, our estimates of the usual on-therapy ranges are more comprehensive and representative than those currently reported in guidelines and product monographs.

Limitations of the study include (1) the relative paucity of data for some dosing regimens, (2) the fact that usual on-therapy ranges do not represent therapeutic ranges, (3) the variation in the outcomes among studies (heterogeneity). In addition, despite attempts to perform sensitivity analyses, these analyses were mostly inconclusive, and we were unable to definitively explore the impact of risk of bias, concern of inapplicability, and differences in laboratory methods on the ranges of drug levels. It is possible that heterogeneity is in part contributed to by differences in the studied populations and methods of measurement. Consequently, it is important for diagnostic laboratories to assess measurement of uncertainty for their assays to guide the interpretation of drug levels.[74–76] If usual on-therapy ranges are used to help in making decisions, it is recommended that laboratories use validated assays that have been calibrated according to current standards.[5,74–76] When providing test results, laboratories may consider taking uncertainty about our usual on-therapy ranges into consideration, for instance, by reporting whether levels fall within the usual on-therapy range, within its 95% CIs, or outside either range.[74] Finally, if the dose is modified because the test falls outside the usual range, we suggest that the assay should be repeated to determine that the dose response is appropriate.

Conclusion

In this systematic review and meta-analysis, we pooled data from 53 studies that collectively included over 30,000 patients to provide updated estimates for the 10th to 90th percentile ranges (i.e., middle 80% of drug levels) for trough and peak concentrations of the four approved DOACs when used in patients with AF using methods commonly used in clinical practice. This update provides clinicians with more representative estimates of the usual on-therapy ranges of DOACs than previously reported, to help guide their decision-making.

What is known about this topic?

- DOACs do not require routine monitoring of drug levels, but measurement of levels might be desirable in some situations.
- In the absence of therapeutic ranges, usual on-therapy ranges (10th to 90th) of drug concentrations are used to interpret measurements.
- Existing guidance documents provide usual on-therapy ranges for drug concentrations, but these have important limitations.

What does this paper add?

- This systematic review and meta-analysis provides updated and more representative usual on-therapy ranges of DOACs levels in patients with AF.

Data Availability Statement

The data underlying this article are provided in **Supporting Information File 6** [available in online version only] and the other Supporting Information Files. The R-syntax underlying this paper will be shared on reasonable request to the corresponding author.

Authors' Contribution

T.A.C.dV., I.U.M., J.H., V.C.B., J.W.E., Q.Y., and N.C.C. have contributed to the concept and design of the study. The protocol including its statistical analysis plan were developed by T.A.C.dV., I.U.M., J.H., V.C.B., J.W.E., N.C.C., and then revised by T.A.C.dV., N.C.C., Q.Y., and S.M. The study was coordinated by T.A.C.dV., I.U.M., and N.C.C. The search strategy was developed by I.U.M., C.G., and N.C.C. I.U.M tailored the search strategy, performed the literature searches, and extracted all data together with C.G. T.A.C. dV., N.C.C., V.C.B., and J.W.E. performed the risk of bias and indirectness assessments and T.A.C.dV. and N.C.C. all other quality assessments. Q.Y. performed all analysis to simulate nonreported values, and T.A.C.dV. all analyses hereafter with support from S.M. T.A.C.dV., I.U.M., J.H., and N.C.C. wrote the initial draft and first subsequent iterations. All the other authors reviewed the drafts, provided critical comments, and revised the initial draft to produce the final manuscript.

Funding

N.C.C. is supported by a Heart and Stroke of Canada New Investigator Award. S.M. was supported by the National Science Foundation Graduate Research Fellowship Program under Grant No. DGE2140743. None of the other authors or their institutions have received funding for this project.

Conflict of Interest

T.A.C.dV. reports nonfinancial support from Daiichi Sankyo and personal fees from Bristol-Myers-Squibb, both outside the submitted work. He also reports that he is a member of the adjudication committee of the Low International Normalized Ratio to Minimize Bleeding with Mechanical Valves (LIMIT) and Direct Oral Anticoagulation versus Warfarin after Cardiac Surgery (DANCE) trials, which are sponsored by the Population Health Research Institute. V.C.B. reports personal fees from Bayer and Pfizer, outside the submitted work. N.C.C. reports personal fees from Stago, Boehringer Ingelheim, and Novo Nordisk, outside the submitted work. J. W.E. reports grants and personal fees from Anthos, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Ionis, Janssen, Merck, and Pfizer, personal fees from USV, during the conduct of the study; grants and personal fees from Anthos, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Ionis, Janssen, Merck, and Pfizer, personal fees from USV, outside the submitted work. The other authors have no conflict of interest to disclose.

Acknowledgment

We thank A. Dayimu for his assistance in utilizing his R-package (i.e., "forestploter"), used to generate the forest plots in this report. The icons used in the graphical abstract were designed by "Freepik," "iconixar," or "Smashicons" from Flaticon.

References

1 Hirsh J, de Vries TAC, Eikelboom JW, Bhagirath V, Chan NC. Clinical studies with anticoagulants that have changed clinical practice. Semin Thromb Hemost 2023;49(03):242–254
2 Hindricks G, Potpara T, Dagres N, et al; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42(05):373–498
3 Steffel J, Collins R, Antz M, et al; External reviewers. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23(10):1612–1676
4 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383(9921):955–962
5 Douxfils J, Adcock DM, Bates SM, et al. 2021 Update of the International Council for Standardization in Haematology recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost 2021;121(08):1008–1020
6 de Vries TAC, Hirsh J, Bhagirath VC, et al. Can a single measurement of apixaban levels identify patients at risk of overexposure? A prospective cohort study. TH Open 2022;6(01):e10–e17
7 Al-Aieshy F, Malmström RE, Antovic J, et al. Clinical evaluation of laboratory methods to monitor exposure of rivaroxaban at trough and peak in patients with atrial fibrillation. Eur J Clin Pharmacol 2016;72(06):671–679
8 Bánovčin P Jr, Škorňová I, Samoš M, et al. Platelet aggregation in direct oral factor Xa inhibitors-treated patients with atrial fibrillation: a pilot study. J Cardiovasc Pharmacol 2017;70(04):263–266
9 Bhagirath VC, Chan N, Hirsh J, Ginsberg J, de Vries TAC, Eikelboom J. Plasma apixaban levels in patients treated off label with the lower dose. J Am Coll Cardiol 2020;76(24):2906–2907
10 Bhagirath VC, Eikelboom JW, Hirsh J, et al. Apixaban-calibrated anti-FXa activity in relation to outcome events and clinical characteristics in patients with atrial fibrillation: results from the AVERROES trial. TH Open 2017;1(02):e139–e145
11 Bolek T, Samoš M, Škorňová I, et al. Dabigatran levels in elderly patients with atrial fibrillation: first post-marketing experiences. Drugs Aging 2018;35(06):539–544
12 Bolek T, Samoš M, Škorňová I, et al. Does proton pump inhibition change the on-treatment anti-Xa activity in xabans-treated patients with atrial fibrillation? A pilot study. J Thromb Thrombolysis 2019;47(01):140–145
13 Bolek T, Samoš M, Stančiaková L, et al. The impact of atorvastatin on dabigatran plasma levels in patients with atrial fibrillation. Blood Coagul Fibrinolysis 2021;32(01):69–71
14 Boonen K, Schmitz E, Rozestraten F, et al. Real life dabigatran and metabolite concentrations, focused on inter-patient variability and assay differences in patients with atrial fibrillation. Clin Chem Lab Med 2017;55(12):2002–2009
15 Chan NC, Coppens M, Hirsh J, et al. Real-world variability in dabigatran levels in patients with atrial fibrillation. J Thromb Haemost 2015;13(03):353–359
16 Chang YT, Hu YF, Liao JN, et al. The assessment of anticoagulant activity to predict bleeding outcome in atrial fibrillation patients receiving dabigatran etexilate. Blood Coagul Fibrinolysis 2016;27 (04):389–395
17 Chaussade E, Hanon O, Boully C, et al. Real-life peak and trough dabigatran plasma measurements over time in hospitalized geriatric patients with atrial fibrillation. J Nutr Health Aging 2018;22 (01):165–173
18 Harenberg J, Du S, Wehling M, et al. Measurement of dabigatran, rivaroxaban and apixaban in samples of plasma, serum and urine, under real life conditions. An international study. Clin Chem Lab Med 2016;54(02):275–283
19 Hirota N, Suzuki S, Yamasaki M, et al. Analysis of bioMARKer distribution and individual reproducibility under rivaroxaban treatment in Japanese patients with non-valvular atrial fibrillation (R-MARK Study, CVI ARO2). Int Heart J 2020;61(04):695–704
20 Horinaka S, Sugawara R, Yonezawa Y, Ishimitsu T. Factor Xa inhibition by rivaroxaban in the trough steady state can significantly reduce thrombin generation. Br J Clin Pharmacol 2018;84 (01):79–87
21 Ji Q, Zhang C, Xu Q, Wang Z, Li X, Lv Q. The impact of ABCB1 and CES1 polymorphisms on dabigatran pharmacokinetics and pharmacodynamics in patients with atrial fibrillation. Br J Clin Pharmacol 2021;87(05):2247–2255
22 Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. Circ J 2015;79(07):1486–1495
23 Lin SY, Kuo CH, Yeh SJ, et al. Real-world rivaroxaban and apixaban levels in Asian patients with atrial fibrillation. Clin Pharmacol Ther 2020;107(01):278–286
24 Lin SY, Tang SC, Kuo CH, et al. Factors affecting serum concentration of dabigatran in Asian patients with non-valvular atrial fibrillation. J Formos Med Assoc 2019;118(07):1154–1160
25 Liu Z, Xie Q, Xiang Q, et al. Anti-FXa-IIa activity test in Asian and its potential role for drug adherence evaluation in patients with direct oral anticoagulants: a nationwide multi-center synchronization study. Cardiovasc Diagn Ther 2020;10(05):1293–1302
26 Martin JL, Esmaeili H, Manuel RC, Petrini M, Wiebe S, Maas H. Pharmacokinetics/pharmacodynamics of dabigatran 75 mg twice daily in patients with nonvalvular atrial fibrillation and severely impaired renal function. J Cardiovasc Pharmacol Ther 2018;23(05): 399–406

27 Mavri A, Vene N, Božič-Mijovski M, et al. Apixaban concentration variability and relation to clinical outcomes in real-life patients with atrial fibrillation. Sci Rep 2021;11(01):13908
28 Miklič M, Mavri A, Vene N, et al. Intra- and inter- individual rivaroxaban concentrations and potential bleeding risk in patients with atrial fibrillation. Eur J Clin Pharmacol 2019;75 (08):1069–1075
29 Mochalina N, Juhlin T, Platonov PG, Svensson PJ, Wieloch M. Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice. Thromb Res 2015;135 (06):1070–1074
30 Mukai Y, Wada K, Miyamoto K, et al. The influence of residual apixaban on bleeding complications during and after catheter ablation of atrial fibrillation. J Arrhythm 2017;33(05):434–439
31 Nakagawa J, Kinjo T, Iizuka M, Ueno K, Tomita H, Niioka T. Impact of gene polymorphisms in drug-metabolizing enzymes and transporters on trough concentrations of rivaroxaban in patients with atrial fibrillation. Basic Clin Pharmacol Toxicol 2021;128(02): 297–304
32 Nissan R, Spectre G, Hershkovitz A, et al. Apixaban levels in octogenarian patients with non-valvular atrial fibrillation. Drugs Aging 2019;36(02):165–177
33 Nosáľ V, Petrovičová A, Škorňová I, et al. Plasma levels of direct oral anticoagulants in atrial fibrillation patients at the time of embolic stroke: a pilot prospective multicenter study. Eur J Clin Pharmacol 2022;78(04):557–564
34 Reilly PA, Lehr T, Haertter S, et al; RE-LY Investigators. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63 (04):321–328
35 Roşian AN, Roşian ŞH, Kiss B, et al. Interindividual variability of apixaban plasma concentrations: influence of clinical and genetic factors in a real-life cohort of atrial fibrillation patients. Genes (Basel) 2020;11(04):438
36 Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015;385(9984):2288–2295
37 Samoš M, Bolek T, Stančiaková L, et al. Anti-Xa activity in oral factor Xa inhibitor-treated patients with atrial fibrillation and a higher risk of bleeding: a pilot study. Blood Coagul Fibrinolysis 2018;29(04):369–373
38 Samoš M, Bolek T, Stančiaková L, et al. Does type 2 diabetes affect the on-treatment levels of direct oral anticoagulants in patients with atrial fibrillation? Diabetes Res Clin Pract 2018; 135:172–177
39 Samoš M, Stančiaková L, Ivanková J, et al. Monitoring of dabigatran therapy using hemoclot thrombin inhibitor assay in patients with atrial fibrillation. J Thromb Thrombolysis 2015;39(01):95–100
40 Schnierer M, Samoš M, Bolek T, et al. The effect of proton pump inhibitor withdrawal on dabigatran etexilate plasma levels in patients with atrial fibrillation: a washout study. J Cardiovasc Pharmacol 2020;75(04):333–335
41 Shin H, Cho MC, Kim RB, et al. Laboratory measurement of apixaban using anti-factor Xa assays in acute ischemic stroke patients with non-valvular atrial fibrillation. J Thromb Thrombolysis 2018;45(02):250–256
42 Shyamkumar K, Hirsh J, Bhagirath VC, Ginsberg JS, Eikelboom JW, Chan NC. Plasma rivaroxaban level to identify patients at risk of drug overexposure: is a single measurement of drug level reliable? TH Open 2021;5(01):e84–e88
43 Silva VM, Scanavacca M, Darrieux F, Cavalheiro C, Strunz CC. Routine coagulation tests in patients with nonvalvular atrial fibrillation under dabigatran and rivaroxaban therapy: an affordable and reliable strategy? Clin Appl Thromb Hemost 2019; 25:1076029619835053
44 Silva VM, Scanavacca M, Darrieux F, Cavalheiro-Filho C, Strunz CC. Effects of rivaroxaban on coagulation tests in patients with nonvalvular atrial fibrillation under real-life conditions. Thromb Res 2017;154:26–27
45 Šinigoj P, Malmström RE, Vene N, et al. Dabigatran concentration: variability and potential bleeding prediction in "real-life" patients with atrial fibrillation. Basic Clin Pharmacol Toxicol 2015;117 (05):323–329
46 Skeppholm M, Al-Aieshy F, Berndtsson M, et al. Clinical evaluation of laboratory methods to monitor apixaban treatment in patients with atrial fibrillation. Thromb Res 2015;136(01):148–153
47 Skeppholm M, Hjemdahl P, Antovic JP, et al. On the monitoring of dabigatran treatment in "real life" patients with atrial fibrillation. Thromb Res 2014;134(04):783–789
48 Skripka A, Sychev D, Bochkov P, et al. Factors affecting trough plasma dabigatran concentrations in patients with atrial fibrillation and chronic kidney disease. High Blood Press Cardiovasc Prev 2020;27(02):151–156
49 Suwa M, Morii I, Kino M. Rivaroxaban or apixaban for nonvalvular atrial fibrillation—efficacy and safety of off-label under-dosing according to plasma concentration. Circ J 2019;83(05): 991–999
50 Suzuki S, Yamashita T, Akao M, Okumura KJ-ELD AF investigators. Clinical implications of assessment of apixaban levels in elderly atrial fibrillation patients: J-ELD AF registry sub-cohort analysis. Eur J Clin Pharmacol 2020;76(08):1111–1124
51 Takatsuki S, Kimura T, Sugimoto K, et al. Real-world monitoring of direct oral anticoagulants in clinic and hospitalization settings. SAGE Open Med 2017;5:2050312117734773
52 Taune V, Wallén H, Ågren A, et al. Whole blood coagulation assays ROTEM and T-TAS to monitor dabigatran treatment. Thromb Res 2017;153:76–82
53 Testa S, Legnani C, Antonucci E, et al; Coordinator of START2-Register. Drug levels and bleeding complications in atrial fibrillation patients treated with direct oral anticoagulants. J Thromb Haemost 2019;17(07):1064–1072
54 Testa S, Tripodi A, Legnani C, et al; START-Laboratory Register. Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: results observed in four anticoagulation clinics. Thromb Res 2016;137:178–183
55 Tomita H, Araki T, Kadokami T, et al; ATTACK-DB research group. Factors influencing trough and 90-minute plasma dabigatran etexilate concentrations among patients with non-valvular atrial fibrillation. Thromb Res 2016;145:100–106
56 Wongcharoen W, Pacharasupa P, Norasetthada L, Gunaparn S, Phrommintikul A. Anti-factor Xa activity of standard and Japan-specific doses of rivaroxaban in Thai patients with non-valvular atrial fibrillation. Circ J 2020;84(07):1075–1082
57 Zhang C, Zhang P, Li H, et al. The effect of dabigatran on thrombin generation and coagulation assays in rabbit and human plasma. Thromb Res 2018;165:38–43
58 Zhu Z, Shen Z, Shi A, et al. Dabigatran plasma concentration indicated the risk of patients with non-valvular atrial fibrillation. Heart Vessels 2022;37(05):821–827
59 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(71):n71
60 McGrath S, Zhao X, Ozturk O, et al. metamedian: an R package for meta-analyzing studies reporting medians. Res Synth Methods 2024;15(02):332–346
61 McGrath S, Sohn H, Steele R, Benedetti A. Meta-analysis of the difference of medians. Biom J 2020;62(01):69–98
62 Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(02):97–111
63 Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Doing Meta-Analysis with R: A Hands-On Guide. 1st ed. Boca Raton, FL and London: Chapman & Hall/CRC Press; 2021

64 Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64(04):380–382
65 Whiting PF, Rutjes AW, Westwood ME, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155(08):529–536
66 de Vries TAC, Hirsh J, Chan NC. Letter by de Vries et al regarding article "off-label under- and overdosing of direct oral anticoagulants in patients with atrial fibrillation: a meta-analysis". Circ Cardiovasc Qual Outcomes 2022;15(05):e008982
67 Shen N-N, Zhang C, Hang Y, et al. Real-world prevalence of direct oral anticoagulant off-label doses in atrial fibrillation: an epidemiological meta-analysis. Front Pharmacol 2021; 12:581293–581293
68 Joosten LPT, van Maanen R, van den Dries CJ, et al. Clinical consequences of off-label reduced dosing of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. Open Heart 2023;10(01): e002197
69 US Food and Drug Administration Rose M, Beasley BN. Center for drug evaluation and research application number: 202155orig1s000 medical review(s). Center For Drug Evaluation And Research 2012;2012:113–115
70 Zhang L, Yan X, Fox KAA, et al. Associations between model-predicted rivaroxaban exposure and patient characteristics and efficacy and safety outcomes in patients with non-valvular atrial fibrillation. J Thromb Thrombolysis 2020;50(01):20–29
71 Zimerman A, Braunwald E, Steffel J, et al. Dose reduction of edoxaban in patients 80 years and older with atrial fibrillation: post hoc analysis of the ENGAGE AF-TIMI 48 randomized clinical trial. JAMA Cardiol 2024;9(09):817–825
72 Joosten LPT, van Doorn S, van de Ven PM, et al. Safety of switching from a vitamin k antagonist to a non-vitamin k antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. Circulation 2023
73 Okumura K, Akao M, Yoshida T, et al; ELDERCARE-AF Committees and Investigators. Low-dose edoxaban in very elderly patients with atrial fibrillation. N Engl J Med 2020;383(18):1735–1745
74 White GH, Farrance IAACB Uncertainty of Measurement Working Group. Uncertainty of measurement in quantitative medical testing: a laboratory implementation guide. Clin Biochem Rev 2004;25(04):S1–S24
75 Gosselin RC, Adcock DM, Bates SM, et al. International Council for Standardization in Haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants. Thromb Haemost 2018;118(03):437–450
76 Gosselin RC, Favaloro EJ, Douxfils J. The myths behind DOAC measurement: analyses of prescribing information from different regulatory bodies and a call for harmonization. J Thromb Haemost 2022;20(11):2494–2506

