Surgery in Practice and Science 15 (2023) 100230

Contents lists available at ScienceDirect

Surgery in Practice and Science

journal homepage: www.sciencedirect.com/journal/surgery-in-practice-and-science

Review Article

Association between direct oral anticoagulant concentrations and clinical outcomes: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Anticoagulation
Therapeutic drug monitoring
Bleeding
Thrombosis

ABSTRACT

Introduction: Current guidelines suggest preoperative direct oral anticoagulant levels of < 30–50 ng/ml. However, there is limited evidence to guide this expert consensus. Reviewing assay titres and clinical outcomes may be able to inform perioperative care of the anticoagulated patient. This review aimed to determine whether DOAC assay plasma concentrations are associated with bleeding or systemic embolic events to better appreciate a possible therapeutic or hazardous reference range.

Methods: Systematic search, performed by an information specialist using a peer-reviewed search. Main search concepts were direct oral anticoagulant therapy for atrial fibrillation or venous thromboembolism. Data synthesised in narrative and tabular format whilst data that could be pooled was subjected to meta-analysis, using a random effects model. Meta regression was conducted for DOAC peak levels and clinical events. PRISMA guidelines were adhered to.

Results: Of 6717 retrieved publications, a total of 17 studies were included in the systematic review and 14 in the meta-analysis/regression. Studies report clinical outcome follow up ranging from 28 to 128 weeks. For every 10 ng/ml increase in DOAC assay trough and peak levels, the mean number of bleeding cases increases by 0.03(95 % CI: –0.32 –0.38, $P = 0.84$) and 0.09(95 %CI: –3.4 –5.3, $P = 0.55$) respectively, the mean number of major bleed cases increases by 0.01(95 %CI: –0.05 –0.07, $P = 0.62$) and 0.011(95 %CI: –0.32 –0.34, $P = 0.74$) respectively and the mean number of systemic embolic event cases decreases by 0.00039(95 %CI: –0.06 –0.0054, $P = 0.88$) and 0.04(95 %CI: –0.56 –0.48, $P = 0.77$) respectively.

Conclusion: There exists no significant, independent relationship, as determined by a univariate meta regression, between DOAC assay concentrations and a patient's risk of bleeding or systemic embolic embolism. This review also highlights the possibility of an absolute, patient specific DOAC assay concentration that may indicate adequate anticoagulation, above which further increases do not confer an increased risk of bleeding. However, further research to characterise this and its utility in the perioperative setting is required.

Introduction

Direct oral anticoagulants (DOACs) represent a major advancement in both the treatment and prevention of thromboembolic events. Fixed dosage regimes of Apixaban, Dabigatran and Rivaroxaban demonstrate favourable rates of ischaemic and haemorrhagic complications when compared with dose adjusted warfarin [1–3]. Consequently, routine laboratory monitoring of DOAC serum concentrations is not encouraged, with no therapeutic or hazardous reference range described beyond a wide 'on therapy' range [4]. Current guidelines for operating on patients

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https://doi.org/10.1016/j.sipas.2023.100230
Received 21 November 2023; Received in revised form 4 December 2023; Accepted 4 December 2023
Available online 6 December 2023

with DOACs utilise pharmacokinetic properties of these agents to promote a time from last dose approach [5,6],. However, the additive pharmacokinetic effects of multiple patient characteristics and comorbidities may impact drug clearance and therefore surgical safety.

Current expert consensus recommends that DOAC concentrations < 30–50 ng/ml are likely to be safe for surgery [7]. The evidence for this is limited to the residual values observed after a time-based interruption protocol, which only reinforces the 24–48 hour post dose window without addressing the impact of DOAC assays [8].. However, validation of this plasma concentration threshold is limited and an agreed therapeutic range has not been established. with limited quality evidence to guide decision making at an individual patient level [7,9],. Validated perioperative measures correlated with perioperative implications are required for clinicians to optimise perioperative patient care, particularly given that accumulating evidence coming from case-reports, observational studies and post-hoc analysis derived from major trials have shown an association between clinical events and DOACs plasma concentrations [10,11],

The need for a hazardous reference range for DOACs is thus currently a matter of intense debate. There is however limited direct evidence regarding DOAC assay titres and clinical outcomes [12]. Further, the necessary controlled trial that would inform perioperative approach to DOAC assay titres has been previously calculated to require at least 10, 000 patients to detect a 20 % relative risk reduction in bleeding with laboratory monitoring compared with standard care [10]. In the interim, sub-analyses of the existing evidence may provide further insights. Accordingly, this systematic review was undertaken to evaluate DOAC assay concentrations and associated clinical outcomes to better appreciate a possible therapeutic, or hazardous, reference range.

Methods and analysis

The methods for this systematic review and meta-analysis, including review question, search strategy, inclusion and exclusion criteria, and risk of bias assessment, are established within this protocol prior to the conduct of the review. The study protocol was prospectively registered with PROSPERO (CRD42022300429). The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) [13] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [14] reporting guidelines.

Search strategy and selection criteria

The Population, Intervention, Comparator group, Outcome (PICO) framework was used to formulate the research question and inclusion criteria. The population was patients prescribed a DOAC for atrial fibrillation or venous thromboembolism. The intervention was a direct oral anticoagulant, rendering comparator null. The outcomes of interest were direct (venous thromboembolism and ischaemic stroke) and indirect (DOAC assay). Only prospective studies that report a trough level were included because the level at which a quantitative assay is sampled should exhibit good correlation between clinical outcome and DOAC exposure [15]. Additionally, trough levels are the most commonly studied (as opposed to peak levels, or area under curves) and clinically, the more logistically amenable test clinicians may request for patients.

The determination of inclusion criteria fulfilment was undertaken in duplicate. The following criteria were required to be met i: Peer review, published, prospective primary method study ii; Patients receiving a DOAC with serum trough level taken iii; Reports an outcome of bleeding or thrombosis iv; available in full text. If a full text was unavailable, attempts to contact the corresponding author were made. Instances of disagreement were resolved through discussion or through the input of a third author as arbiter. Any study reporting metrics was converted to weeks. To avoid confounding, studies were excluded if the population is comprised of patients under the age of 18 years, a cases series (population $n < 30$), or if the study had an inappropriate design that does not produce observational data.

The literature search was performed by an information specialist (JHWJ) using a peer-reviewed search strategy (Supplementary Information).

Data extraction and analysis

Two reviewers independently screened titles and abstracts, review full texts, and extracted individual patient-level data using a standard extraction form. Screening of titles and abstracts was facilitated through use of a web application (Rayyan, Qatar Computing Research Institute, Ar-Rayyan, Qatar) [16]. Disagreements were resolved by consensus, with a third reviewer acting as arbitrator as required. Extracted datapoints included year of publication, study design, duration, cohort characteristics, intervention characteristics and outcome data. When apixaban and rivaroxaban concentrations were reported as international units, data was converted to anti factor Xa activity by using the following formula: 1 IUnit/ml = 225 ng/ml [17]. When DOAC assays were presented as both Liquid Chromatography-Mass Spectrometry (LC-MS) or Anti-Factor Xa levels, LC-MS was prioritised, although evidence demonstrates good correlation between these two methods [18]. Data was synthesised in narrative and tabular formats. The primary outcomes of interest were bleeding or systemic embolic embolism (pulmonary embolism, cerebrovascular ischaemic stroke, deep vein thrombosis [SEE]). Other outcomes of interest included severity of bleed and death. Two reviewers independently performed risk of bias assessments with non-randomised observational studies critically appraised using the Downs and Black checklist [19].

Statistical analysis

Mean and standard deviation of DOAC trough and peak levels were pooled across the studies using a random effects meta-analysis model to generate a mean value. However, studies that required calculation of a combined mean and combined standard deviation due to the presentation of data were not included in meta regressions. The I^2 statistic was used to evaluate heterogeneity (with $I^2 > 50$ % indicating significant heterogeneity) as was Cochran's Q P value (with p value < 0.05 indicating significant heterogeneity). A variable was included in the meta-analysis if at least 2 studies were available for analysis.

Where possible, measures of central tendency were standardised to mean values (see computational procedure in Supplemental Information). As the effect of dose was not of concern, doses were not compared and studies with multiple doses of the DOACs had the dose groups combined with mean values in proportion to sample size of each group. The outcomes were regressed against trough and peak values in separate univariate linear regressions. Computational procedure is disclosed in supplementary information. Data analyses were performed using Stata Statistical Software: Release 15.1 College Station, TX: StataCorp LP. A p value of < 0.05 denoted statistical significance.

Results

Our search identified a total of 6717 records. There were 5826 unique studies after duplicate removal (Supplemental Information). During the search process, 10 full texts were unavailable. In total, 17 studies were included in this systematic review. Characteristics of the included studies are detailed in Table 1. Study publication year ranged from 2014 to 2022. All included articles were prospective observational cohort studies and took serum measurements at steady state, with a mean clinical outcome follow up of 62.8 weeks (SD 25.1), range 28 to 128 weeks. The most common indication for commencing a DOAC was non-valvular atrial fibrillation. A total of four studies investigated apixaban, six studies investigated rivaroxaban and nine studies investigated dabigatran. The concomitant use of antiplatelets was inconsistently reported and rates range from 0 % [20,21], to 24.4 % [22]. Results

Table 1
Study characteristics.

First author	Year	Country	Indication	Duration of follow Up (weeks)	Max cohort Size	Females / Males (%)	CHADSVASC mean (SD)	HASBLED mean (SD)	DOAC	Bleeding definition
Bhagirath, V [24]	2017	Canada	NVAF	53	2392	41 / 59	ND	ND	Apixaban	ISTH
Suzuki, S [22]	2020	Japan	NVAF	52	943	45.5 / 54.5	4.4(1.2)[a]	2.5(0.9)	Apixaban	"bleeding requiring hospitalisation"
Osanai [25]	2015	Japan	NVAF	38	124	50 / 50	2.7(0.8)[a]	ND	Apixaban	ISTH
Testa [26]	2018	Italy	NVAF	52	208	44.7 / 55.3	3.0(2.3)[b]	ND	Apixaban	ND
				52	172	44.8 / 55.2	3.0(1.8)[b]	ND	Rivaroxaban	
				52	185	43.2 / 56.8	3.0(1.8)[b]	ND	Dabigatran	
Chang, Y [27]	2016	Taiwan	AF & VTE	52	208	32.1 / 67.9	3.6(1.3)[b]	1.8(1.0)	Dabigatran	ISTH
Chaussade, E [23]	2018	France	NVAF	52	68	76.5 / 23.5	4.8(1.4)[b]	1.8(0.7)	Dabigatran	ISTH
Lin, S [21]	2019	Taiwan	AF	98	46	71.7 / 28.3	4.5(1.2)[b]	2.6(0.8)	Dabigatran	PLATO
Mochalina, N [20]	2015	Sweden	AF	52	33	48.5 / 51.5	2.3(1.3)[b]	1.6(0.9)	Dabigatran	ISTH
Reilly, P [15]	2014	USA	AF	104	8449	34.7 / 65.3	ND	ND	Dabigatran	ISTH
Skripka, A [28]	2020	Italy	NVAF	38	60	55 / 45	4.0(1.3)[b]	2.0(1.5)	Dabigatran	ND
Sychev, D [29]	2020	Russia	AF	64	96	59.3 / 40.7	3.0(1.8)[b]	1.0(1.5)	Dabigatran	ISTH
Zhu, Z [30]	2022	Japan	NVAF	72	86	57 / 43	3.4(1.7)[b]	1.2(0.9)	Dabigatran	ISTH
Miklic, M [31]	2019	Sweden	AF	80	60	46.7 / 53.3	2.2(1.3)[a]	1.1(0.6)	Rivaroxaban	ND
Sakaguchi, T [32]	2017	Japan	NVAF	128	94	34/ 66	2.0(1.4)[a]	NDA	Rivaroxaban	ISTH
Sychev, D [33]	2020	Russia	NVAF	86	128	75 / 25	6.0(1.5)[b]	2.0(0.8)	Rivaroxaban	ISTH
Wada, S [34]	2019	Japan	NVAF	27	114	36.8 / 63.2	2.3(1.1)[a]	2.1(0.8)	Rivaroxaban	ISTH
Zalewski, J [35]	2020	Poland	VTE	40	132	60 / 40	ND	ND	Rivaroxaban	ISTH

NVAF = Non valvular AF, VTE = Venous Thromboembolism. ISTH = International Society of Thrombosis & Haemostasis. ND = Not Disclosed
[a] =CHADS2.
[b] CHADS2VASC, ND = Not disclosed, ISTH = definition consistent with International Society of Thrombosis and Haemostasis.

of included studies were presented in two ways; plasma DOAC titres of a cohort with outcomes as a proportion of the population or, mean plasma DOAC titres of groups who did and did not experience an outcome of interest. Only one study included patients with cancer and accounted for 8.8 % of the included cohort [23]. Risk of bias analysis of the included studies demonstrated that the majority of studies were of moderate risk of bias.

DOAC assay troughs and outcomes

Apixaban

Apixaban trough levels ranged from a minimum of 111 ng/ml (SD = 123.3) [26] to 208 ng/ml(SD=134.4) [25]. The overall mean Apixaban trough level was 106.9 ng/ml (95 % confidence interval (CI): 100.0, 113.9) with no heterogeneity (I^2=0, Cochran's Q P value=0.602) (Fig. 1a).

Bleeding rates for patients prescribed Apixaban ranged from 5.6 % [25] to 10.9 % [24], major bleeding from 1.42 % [24] to 1.8 % [22] and SEE rates from 1.88 % [24] to 0.96 % [26]. Bhagirath et al. [24] discerned patients with the lowest decile (assay level < 50 ng/ml) had a significantly higher risk of stroke than those with higher DOAC assay levels (Fisher's exact test, $p = 0.013$). Bhagirath et al. [24] also noted a significant association between DOAC assay level and occurrence of bleeding (cox regression, $p = 0.01$). SEE occurred in patients with Apixaban levels as high as 113 ng/ml [26]. There was no other significant association between Apixaban DOAC assay and clinical outcome in the included studies.

Dabigatran

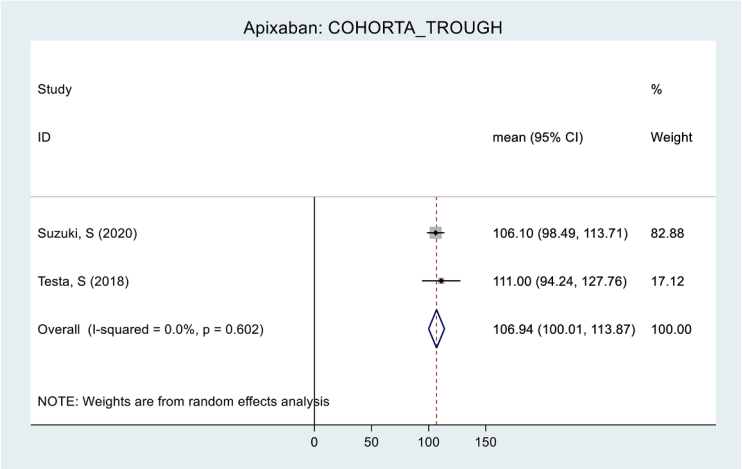
Dabigatran trough levels ranged from a minimum of 51.3 ng/ml (SD = 38.6) [30] to 127.3 ng/ml(SD = 156.9) [29]. The overall mean Dabigatran trough level was 88.1 ng/ml(95 % CI: 69.9, 106.4) with high heterogeneity (I^2 = 92.6 %, Cochran's Q P value=0.000).(Fig. 1b)

Bleeding rates in patients treated with Dabigatran ranged from 2.17 % [21] to 27.15 % [15], major bleeding rates ranged from 1.92 % [27] to 5 % [28] and SEE rates, 0 % [20,28,29], to 15.12 % [30]. In a Kaplan-Meier analysis, Dabigatran levels greater than 117.7 ng/ml were associated with higher rates of bleeding (15.4 % vs 4.9 %, $P = 0.01$) [27]. Chaussade [23] similarly found, through Kaplan-Meier evaluation, that above a trough threshold of 200 ng/ml, bleeding risk is significantly increased (log rank tests=0.0003) and 90th percentiles of trough concentrations (243.9 ng/ml) had a 98 % specificity (95 %CI 0.95–1.00) and 54 % sensitivity (95 %CI 0.23–0.77) for predicting bleeding events. Trough concentrations in patients who experienced a bleed were noted to be 1.57x higher than their non-bleeding counterparts (74.96 ng/ml vs. 47.61 ng/ml, $P = 0.008$) and 2.56x higher for major bleeding vs no major bleeding (122.06 ng/ml vs. 47.61 ng/ml, $P = 0.007$)) [30]. A bleeding event occurred in a patient with nadir trough of 35.9 ng/ml (haematuria) [29]. Further, the trough concentrations in patients with a stroke was noted to be significantly lower than those who did not experience an SEE (27.06 ng/ml vs. 60.39 ng/ml, $P = 0.033$) [30] but did also occur in patients with levels as high as 91 ng/ml [26]. This observation was also observed by Reilly et al's study which demonstrated a bi-directional relationship between Dabigatran trough values and outcomes [15]. Here, the risk of ischaemic events was inversely related to trough dabigatran concentrations ($p < 0.045$) whilst multiple logistic regression (c-statistic 0.715, 95 % CI:0.69 to 0.74) showed major bleeding risk increased with dabigatran exposure ($p < 0.0001$) [15].

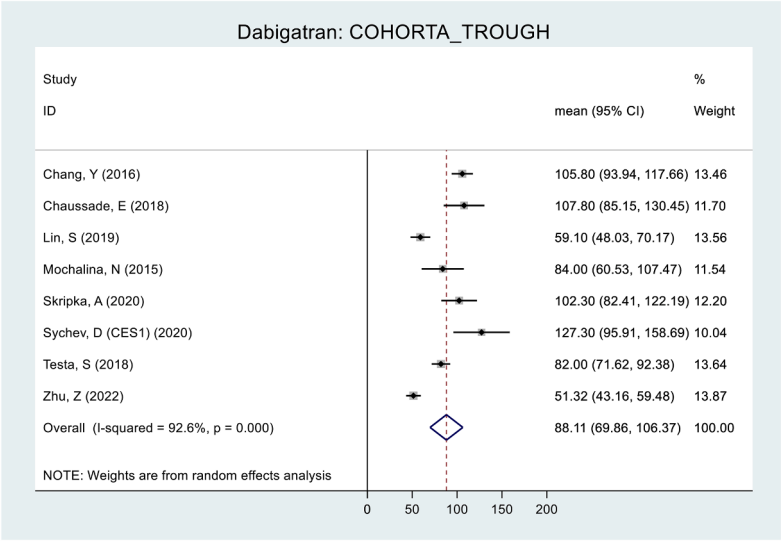
Rivaroxaban

Rivaroxaban trough levels ranged from 20.9 ng/ml(SD=14.2) [34] to 52.3 ng/ml(SD=13.3) [33]. The overall mean Rivaroxaban trough level was 37.4 ng/ml(95 % CI: 17.6, 57.2) with high heterogeneity (I^2 = 99.0 %, Cochran's Q P value=0.000).(Fig. 1c)

1a) Apixaban Trough Levels



1b) Dabigatran Trough Levels



1c) Rivaroxaban Trough Levels

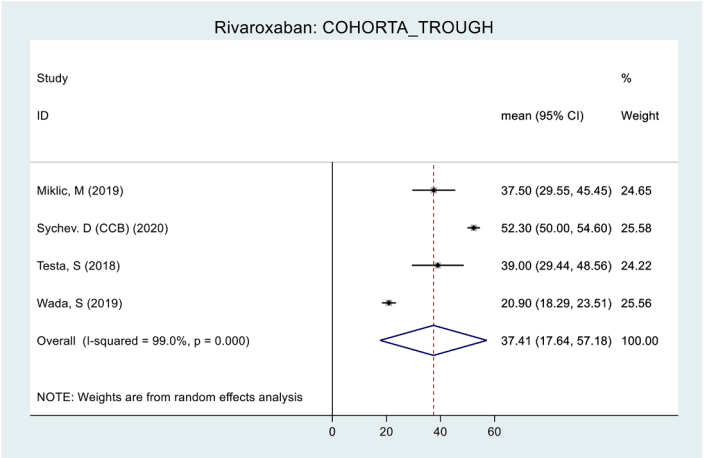


Fig. 1. Meta analysis of DOAC trough levels.

Bleeding rates in those prescribed Rivaroxaban ranged from 20.4 % [35] to 46.67 % [31] with major bleeding rates ranging from 5 % [31] to 8.24 % [34] and SEE rates ranging from 1.74 %(24) to 23.33 % [33]. SEE occurred in patients with a trough level as high as 91 ng/ml(31) and bleeding in levels as low as 6 ng/ml [34]. Patients with bleeding were noted to have higher trough concentrations than those who did not by Miklic et al. [31] (48 ng/ml(SD=30) vs 34 ng/ml(SD=26), $p = 0.02$). No other significant associations between Rivaroxaban trough levels and clinical outcomes were observed in the included studies.

DOAC assay peak and outcomes

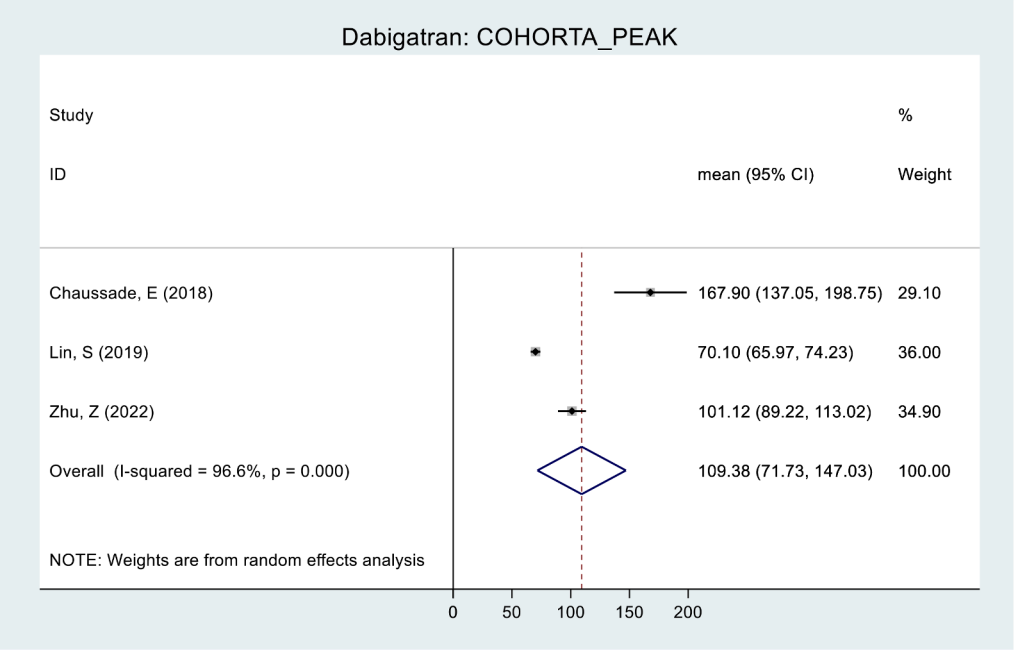
Apixaban

Apixaban peak levels were reported in one study, so a meta regression was not performed. This study demonstrated a mean plasma peak of 409.2 ng/ml(SD = 167.3) [25]. There was no significant difference in peak levels between patient who did and did not experience a bleeding event (445.5 ng/ml(SD = 141.8) VS 407.3(SD = 168.8), $P = 0.49$) [25].

Dabigatran

Dabigatran peak levels were assessed in three studies [21,23,30], with a range of 70.1 ng/ml(SD=14.3) [21] to 167.9 ng/ml(SD = 129.8) [23]. The overall mean Dabigatran peak level was 109.4 ng/ml (95 %CI: 71.7, 147.0) with high heterogeneity ($I^2 = 96.6$ %, Cochran's Q P value

2a) Dabigatran Peak Levels



2b) Rivaroxaban Peak Levels

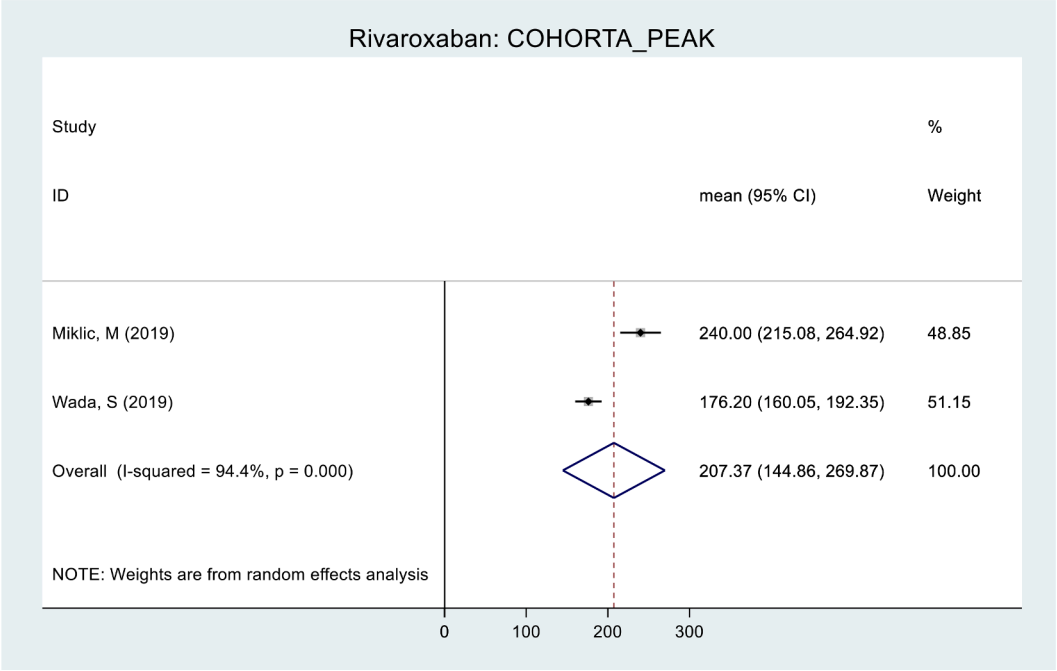


Fig. 2. Meta analysis of DOAC peak levels.

= 0.00) (Fig. 2a). No significant association between peak Dabigatran level and clinical outcome was observed in the included studies.

Rivaroxaban

Rivaroxaban peak levels were assessed in three studies [31,32,34], two of which were included in the meta-regression. The mean peak level ranged from 176,2 ng/ml(SD = 88)(31) to 438.8 ng/ml (SD = 182.3). The overall mean Rivaroxaban peak level is 207.4 ng/ml (95 % CI:144.9, 269.9) with high heterogeneity (I^2 = 94.4 %, Cochran's Q P value = 0.000)(Fig. 2b). The mean peak Rivaroxaban assay level was significantly higher in patients with bleeding events than in those without (540 ng/ml(SD = 157.5) VS 416.3 ng/ml(SD = 180), P = 0.001) [32].

Meta regression

Apixaban

There was insufficient data to undertake a meta regression on Apixaban levels and either bleeding or SEE events.

Dabigatran

A total of 8 studies including 782 patients was used in the Dabigatran assay trough meta regression and 3 studies including 200 patients for the Dabigatran assay peak meta regression.

For every 1 ng/ml increase in Dabigatran trough level, the mean number of bleeding cases increases by 0.93 (Mean Difference = 0.93, 95 % CI −4.75, 6.60, P value = 0.67) and mean number of SEE events decreases by 3.28 (Mean Difference = 3.28, 95 % CI 6.78, 0.22, P value=0.062). For every 1 ng/ml increase in Dabigatran peak level, the mean number of bleeding cases increases by 3.533 (Mean Difference = 3.53, 95 % CI −39.58, 46.66, P value = 0.49) and incidence of SEE decreases by 1.54(95 % CI −81.13, 78.06. P value = 0.85).

Rivaroxaban

A total of 4 studies including 434 patients was used in the Rivaroxaban assay trough meta regression. For every 1 ng/ml increase in Rivaroxaban trough level, the mean number of bleeding cases increases by 1.06 (Mean Difference = 1.06, 95 % CI −10.80, 12.92, P value = 0.46). There was insufficient studies to conduct a meta regression on Rivaroxaban peak levels and bleeding, or Rivaroxaban levels and SEE.

Discussion

This review aimed to investigate the association of DOAC assay concentrations on patient's clinical outcomes and thus make inferences on the perioperative approach to anticoagulated patients. The results confirm existing knowledge that there is a significant inter-individual variation in pharmacokinetic response and DOAC assay levels [4]. The univariate linear regression of DOAC trough and peak concentrations demonstrates negligible, non-significant associations with haemostatic or thromboembolic outcomes. Whilst isolated studies have found significance in a concentration-outcome response relationship, the meta regression suggests at a populace level, this is less significant. Previous consortiums have proposed a complex relationship between patient characteristics, covariates, DOAC levels and clinical outcome, where factors such as elderly age, weight, variable bioavailability, hepatic and renal function increase bleeding risk directly and indirectly through associations with higher DOAC assay levels [36]. If this hypothesis were true, and an increased risk of bleeding were related (directly or indirectly) to higher DOAC assay levels, we should have observed a more significant relationship between DOAC assay levels and clinical outcomes.

Whilst the meta-regression results suggest no influence on increasing DOAC assay titres and long-term outcomes, careful interpretation of these results, in a greater context is required. Indiscriminate extrapolation of the results would suggest that a DOAC assay titre value of 1–2 ng/ml confers no more significant risk for SEE than titres values of 1000–2000 ng/ml. Superficially, these results stand in contrast to previously published reviews in this area, which suggest a more significant association between DOAC assay titres and safety/ efficacy [11]. However, when examined within context, the results instead offer support to the potential notion of significant, patient specific values, within which a therapeutic range does exist [11]. The totality of existing, moderate quality, evidence suggests that there may be certain DOAC assay thresholds, between which an optimal balance of anticoagulation and safety is observed. These values are likely patient specific, influenced and heavily modulated by their own specific clinical characteristics (age, weight, hepatorenal function, polypharmacy interactions, absorption) and not generalisable, absolute values. These theoretical threshold values for a majority of patients likely lie between 12 and 61 ng/ml and < 200 ng/ml, depending on the aforementioned factors [11, 37], So whilst this review does not specifically support the use of DOAC assay testing for risk stratification long term, or dose titration according to DOAC assay concentrations, it emphasises the need for further characterising this potential patient specific threshold and it's impacts on perioperative care and surgical triage.

DOACs produce a 10 % reduction in all-cause mortality, irrespective of dose, when compared with warfarin (RR 0·90, 0·85–0·95; p = 0·0003) [38]. Notably, lower doses were responsible for significantly more ischaemic strokes (RR 1·28, 1·02–1·60; p = 0·045) but demonstrated similar reduction in all strokes/ SEE (RR 1·03, 0·84–1·27; p = 0·74) and less bleeding events (RR 0·65, 0·43–1·00; p = 0·05) than warfarin. This suggests that the existing fixed dosage regimes are already close to providing the 'optimal' balance and further titration according to DOAC assay concentration is fruitless. This observation is congruent with the lack of direct support meta-regression results provide for titrating DOAC dose according to pharmacokinetic values. Instead, the benefit for routine DOAC assay monitoring is potentially highest in patients who are anticipated to have trough levels significantly different from the majority of the population (or < 12–61 ng/ml, < 200 ng/ml), based on a culmination of the aforementioned clinical characteristics.

This review has several limitations. This is a meta-regression on aggregate data, therefore, associations between average patient characteristics and the pooled treatment effect may not necessarily reflect true, or underestimate, associations between the individual patient-level characteristics and treatment effect. Such inherent limitations include how assessment of DOAC assay concentrations did not control for concomitant confounding medications, such as amiodarone, proton pump inhibitors, calcium channel blockers, anti-epileptics and issues like compliance. Another limitation is the limited representation of people with clinical characteristics that may benefit from DOAC assay monitoring, such as extremes of body weight (< 50 kg or > 120 kg) and end stage renal failure. Further, a composite meta-regression of all anticoagulants (both Factor II and Factor Xa inhibitors) was reported. This methodological approach is however principally supported by existing evidence that reference both Dabigatran and Rivaroxaban/Apixaban together in the reference range for perioperative analysis and the theoretical continuous risk spectrum of DOAC assay titre and bleeding events [39]. This review also only included peer reviewed, published literature. The inclusions of other sources may have provided further insight, such as the Boehringer Ingelheim (Dabigatran manufacturer) internal correspondence. Highlighted by a British Medical Journal investigation, these documents, released during a U.S litigation, suggested that an optimal benefit-risk ratio for Dabigatran was achieved when trough levels were within 40–215 ng/ml [40]. Lastly, most of the included studies analysed DOAC assay concentrations at distance from the clinical event, however all studies assessed concentrations after enough doses to achieve steady state.

Conclusion

This systematic review, meta-analysis and meta regression summarises the existing evidence on DOAC assays to characterise their

influence on clinical outcomes. There exists a wide inter-individual variation in trough and peak levels across all DOAC medications. However, there exists no significant, independent, univariate relationship, between DOAC assay concentrations and a patient's risk of bleeding or SEE. This review also highlights the possibility of an absolute, patient specific DOAC assay concentration that may indicate adequate anticoagulation, above which surgery should be delayed, below which it may be safe to proceed. However, further research to characterise this and its' utility is urgently required.

Ethics approval and consent to participate

Ethical approval was not required or sought for this manuscript due to the secondary nature as a review of pre existing literature.

Consent for publication

All authors have consented to the publication of this manuscript.

Author contributions (Ensure all authors are referred to in the statement)

All authors contributed to the study conception and design. Specifically, material preparation, data collection and analysis were performed by Brandon Stretton, Jonathon Henry W. Jacobsen, Phillip Harford, Jaspreet Sandhu and Suzanne Edwards. The first draft of the manuscript was written by Brandon Stretton and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CRediT authorship contribution statement

Brandon Stretton: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Philip Harford:** . **Joshua Kovoor:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Stephen Bacchi:** . **Aashray Gupta:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Jaspreet Sandhu:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Hollie Moran:** . **Suzanne Edwards:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jonathon Henry W. Jacobsen:** . **Guy Maddern:** . **Mark Boyd:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated during and/or analysed during the current study are available in the aforementioned repositories (as listed in the methods section).

Funding

No funding to declare

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sipas.2023.100230.

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