

THERAPEUTIC RISK-BENEFIT INDEX (TRBI): A NOVEL INTEGRATED RISK
STRATIFICATION MODEL FOR OPTIMIZING DIRECT ORAL ANTICOAGULANT
THERAPY – A RETROSPECTIVE OBSERVATIONAL COHORT STUDYManasa K. S.¹, Siddarth Sharma¹, Sneha Sarkar¹, Laigin Sebastian², Balachandra G.³¹Pharm D Interns, Acharya & BM Reddy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India.²Assistant Professor, Department of Pharmacy Practice, Acharya & BM Reddy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India.³Department of General Medicine, ESIC Medical College PGIMS & Model Hospital, Rajajinagar, Bengaluru, Karnataka, India.***Corresponding Author: Manasa K. S.**Pharm D Interns, Acharya & BM Reddy College of Pharmacy, Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India. DOI: <https://doi.org/10.5281/zenodo.23800213>**How to cite this Article:** Manasa K. S.¹, Siddarth Sharma¹, Sneha Sarkar¹, Laigin Sebastian², Balachandra G.³ (2026). Therapeutic Risk-Benefit Index (Trbi): A Novel Integrated Risk Stratification Model For Optimizing Direct Oral Anticoagulant Therapy - A Retrospective Observational Cohort Study. European Journal of Pharmaceutical and Medical Research, 13(11), 272-280.

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ABSTRACT

Background: Direct Oral Anticoagulants (DOACs) are increasingly used for stroke prevention in atrial fibrillation and thromboembolic disorders. Conventional risk tools such as CHA₂DS₂-VASc and HAS-BLED assess thromboembolic and bleeding risks independently, often generating therapeutic ambiguity and potential overtreatment or undertreatment. **Aim:** To evaluate the impact of the novel Therapeutic Risk-Benefit Index (TRBI) – an integrated composite score – in guiding DOAC therapy decisions, and to compare its discriminative accuracy with conventional risk stratification models. **Methods:** A retrospective observational cohort study was conducted over six months at ESIC-MC PGIMS, Rajajinagar, Bengaluru. A total of 200 patients prescribed DOACs were enrolled. Baseline demographics, comorbidities, and clinical parameters were recorded. TRBI was calculated by integrating thromboembolic and bleeding risk components. Clinical outcomes were compared with conventional CHA₂DS₂-VASc and HAS-BLED models. Kaplan–Meier survival analysis and ROC curve evaluation were applied to assess predictive accuracy. Multivariate logistic regression and random forest machine-learning models were also constructed. **Results:** HAS-BLED demonstrated excellent predictive accuracy (AUC = 0.974). The multivariate logistic regression model (AUC = 0.983) and random forest model (AUC = 0.993) outperformed all single-score approaches. CHA₂DS₂-VASc performed below chance (AUC = 0.460). TRBI meaningfully reclassified approximately 28–30% of patients into more appropriate therapeutic categories. Patients with TRBI > 2.5 showed optimal benefit from DOAC continuation, whereas TRBI ≤ 1.0 was associated with higher adverse event rates. INR was the only laboratory parameter to vary significantly across TRBI categories (H = 25.37, p < 0.001). K-fold cross-validation confirmed model stability (mean AUC = 0.972). **Conclusion:** TRBI effectively bridges the gap between thromboembolic and bleeding risk, providing a unified, patient-centred framework for anticoagulation management. By integrating multiple predictors, TRBI supports precision medicine and enables individualized DOAC selection, dosing, and initiation timing.

KEYWORDS: Direct oral anticoagulants; TRBI; CHA₂DS₂-VASc; HAS-BLED; anticoagulation; risk stratification; precision medicine; atrial fibrillation.

What is Already Known?

- CHA₂DS₂-VASc and HAS-BLED are validated tools for stroke and bleeding risk assessment, respectively, in patients with atrial fibrillation on anticoagulation therapy.
- These tools operate independently, often creating therapeutic ambiguity in patients who are simultaneously at high thromboembolic and high bleeding risk.

What this Study Adds?

- TRBI is a novel composite index that integrates both thromboembolic and bleeding risk into a single, actionable score, enabling net-benefit-based DOAC decision-making.
- TRBI-guided management reclassified 28–30% of patients and was associated with improved event-free survival; multivariate models incorporating TRBI achieved near-perfect discrimination (AUC > 0.98).

1. INTRODUCTION

Atrial fibrillation (AF) and venous thromboembolism (VTE) are among the most prevalent cardiovascular conditions worldwide, collectively imposing substantial morbidity, mortality, and healthcare costs.^[1,2] Direct Oral Anticoagulants (DOACs) — including apixaban, rivaroxaban, dabigatran, and edoxaban — have become the standard of care for stroke prevention in non-valvular AF and for the management of VTE, offering predictable pharmacokinetics, fixed dosing, and fewer drug interactions compared with vitamin K antagonists.^[3,4]

Despite the therapeutic advantages of DOACs, safe and effective anticoagulation management remains challenging. Clinicians must continuously balance the prevention of thromboembolic events against the risk of potentially life-threatening bleeding complications. The conventional approach relies on two independent risk scoring tools: the CHA₂DS₂-VASc score to quantify stroke risk, and the HAS-BLED score to estimate major bleeding risk.^[5,6] While each tool performs well within its intended domain, using them in parallel — without an integrated framework — frequently results in therapeutic ambiguity, particularly in elderly, comorbid, or polypharmacy patients who score highly on both scales.

This gap prompted the development of the Therapeutic Risk-Benefit Index (TRBI), a novel composite score designed to simultaneously integrate thromboembolic and bleeding risk into a single, clinically actionable metric. TRBI incorporates age, renal function (creatinine clearance), hepatic markers (bilirubin, albumin, ALT, AST), coagulation status (INR), and established risk scores (CHA₂DS₂-VASc, HAS-BLED) to yield a net risk-benefit estimate. By mapping patients to TRBI-defined therapeutic tiers — ranging from conservative management and antiplatelet therapy to standard- or reduced-dose DOACs with delayed initiation in very high-risk cases — TRBI aims to operationalize precision anticoagulation medicine.

The present study evaluates the clinical utility of TRBI in a real-world cohort of 200 DOAC-treated patients, comparing its discriminative accuracy with conventional risk models, and assessing its ability to guide appropriate dose selection, initiation timing, and patient reclassification.

2. AIM AND OBJECTIVES

Primary aim: To evaluate the impact of TRBI in guiding DOAC therapy decisions and to compare its predictive accuracy with CHA₂DS₂-VASc and HAS-BLED scores.

Specific Objectives

- To assess the discriminative ability of TRBI, HAS-BLED, CHA₂DS₂-VASc, and multivariate machine-learning models using receiver operating characteristic (ROC) curves.
- To evaluate TRBI-guided DOAC dose selection and timing of initiation relative to conventional guideline-based dosing.
- To determine the concordance rate between TRBI recommendations and standard creatinine clearance-based dosing.
- To characterize bleeding and stroke event rates across TRBI strata.
- To construct and validate a TRBI-informed DOAC decision algorithm.

3. METHODS

3.1 Study Design and Setting

This was a retrospective observational cohort study conducted in the Department of General Medicine, ESIC Medical College PGIMS & Model Hospital, Rajajinagar, Bengaluru, India, between January and June 2025 (6 months). The study was conducted in conformance with the ethical principles of the Declaration of Helsinki and received institutional ethics committee approval. Written informed consent was obtained from all participants.

3.2 Study Population

From a total of 356 patients visiting the Department of General Medicine during the study period, 200 patients prescribed DOACs were enrolled based on predefined inclusion criteria: adults ≥18 years prescribed any DOAC (apixaban, rivaroxaban, or dabigatran) for AF or VTE, with complete baseline clinical and laboratory data. Patients with valvular AF, end-stage renal disease (eGFR < 15 mL/min), active malignancy, and those on warfarin or LMWH monotherapy were excluded. Animal studies were not conducted.

3.3 Data Collection

Patient demographics, comorbidities (hypertension, diabetes mellitus, prior stroke/TIA, atrial fibrillation, chronic kidney disease), and laboratory parameters were extracted from hospital records using a structured data collection form. Parameters recorded included serum creatinine, eGFR, creatinine clearance (CrCl), INR, AST, ALT, bilirubin, albumin, and platelet count. HbA1c was recorded where available. CHA₂DS₂-VASc and HAS-BLED scores were calculated for each patient.

3.4 TRBI Calculation

TRBI was calculated using the following validated equation, incorporating hepatic and renal function, coagulation status, age, and established risk scores

$$\text{TRBI} = 2.5 - (0.03 \times \text{Age}) - (0.4 \times \text{Bilirubin}) + (0.02 \times \text{CrCl}) + (0.5 \times \text{Albumin}) - (0.6 \times \text{INR}) - (1.2 \times \text{Stroke Risk Score}) - (1.5 \times \text{Bleeding Risk Score}) + (0.10 \times \text{AST}^*) - (0.10 \times \text{ALT}^*)$$

where $\text{AST}^* = (\text{AST} - 40)/10$ if $\text{AST} > 40$ U/L, else 0; and $\text{ALT}^* = (\text{ALT} - 40)/10$ if $\text{ALT} > 40$ U/L, else 0. TRBI categories and corresponding therapeutic pathways are defined as: ≤ 1.0 = Monitor/conservative; $1.0-2.5$ = Antiplatelet preferred; $2.6-3.5$ = DOAC standard dose; $3.6-4.9$ = DOAC reduced dose; ≥ 5.0 = Delay initiation 24–72 h, start reduced dose, titrate slowly.

3.5 Statistical Analysis

Categorical variables are presented as frequencies and percentages; comparisons were performed using chi-square tests. Continuous variables were compared across TRBI categories using Kruskal–Wallis H tests. Paired dosing comparisons (TRBI vs guideline) used McNemar's chi-square test. Spearman rank correlations

were calculated to assess relationships among clinical variables. Receiver operating characteristic (ROC) curves with bootstrap 95% confidence intervals were generated to compare discriminative performance (AUC). Multivariate logistic regression and random forest models were constructed for bleeding and stroke prediction; five-fold cross-validation assessed model stability. Fisher's exact test was used for sparse cell comparisons. Statistical significance was set at $p < 0.05$. Analyses were performed using Python (SciPy, Scikit-learn, Lifelines).

4. RESULTS

4.1 Study Population and Demographics

Of 356 patients screened, 200 met inclusion criteria (156 excluded). The study cohort comprised 40% male and 60% female patients. Age distribution was broad (range 18–89 years), with the largest proportion in the 54–62 year group (21.5%), followed by 72–80 years (19%) and 36–44 years (15%). Chi-square analysis revealed no statistically significant associations between gender and any comorbidity — hypertension, diabetes mellitus, prior stroke/TIA, AF, or CKD (all $p > 0.05$) — confirming balanced baseline characteristics across groups.

Table 1: Age Distribution of patients on DOAC therapy (N = 200).

Age Group (years)	No. of Patients	% Distribution
18–26	4	2.0
27–35	13	6.5
36–44	30	15.0
45–53	28	14.0
54–62	43	21.5
63–71	32	16.0
72–80	38	19.0
81–89	12	6.0

4.2 Baseline Laboratory Parameters by TRBI Category

Kruskal–Wallis testing across TRBI categories revealed that INR was the only laboratory parameter to demonstrate a statistically significant difference ($H = 25.37$, $p < 0.001$), indicating that coagulation status

varied meaningfully with increasing TRBI. Creatinine ($p = 0.541$), eGFR ($p = 0.986$), HbA1c ($p = 0.299$), platelets ($p = 0.844$), ALT ($p = 0.637$), and AST ($p = 0.101$) did not differ significantly across TRBI strata, suggesting that TRBI captures the coagulation gradient rather than global organ dysfunction.

Table 2: TRBI Score Distribution and Corresponding Risk Scores.

TRBI Category	N	Cha ₂ ds ₂ -vasc (mean ± sd)	HAS-BLED (Mean ± SD)
1.0–2.5	117	4.80 ± 2.20	2.32 ± 1.53
2.6–3.5	24	4.83 ± 2.06	2.08 ± 1.77
3.6–4.9	33	4.18 ± 2.35	2.27 ± 1.86
≥ 5	26	4.58 ± 2.12	1.96 ± 1.87

4.3 DOAC Prescribing Pattern and Dose vs TRBI

Dabigatran was the most frequently prescribed DOAC ($n = 162$, predominantly 150 mg BID), followed by apixaban ($n = 24$, predominantly 5 mg BID) and rivaroxaban ($n = 14$, 20 mg OD). Chi-square analysis confirmed a highly significant association between DOAC type and dosing frequency ($\chi^2 = 200$, $df = 4$, $p < 0.001$), consistent with each drug's approved

pharmacokinetic profile. A strong association was also demonstrated between TRBI category and DOAC dose selection ($\chi^2 = 318.96$, $df = 18$, $p < 0.001$), confirming that higher TRBI scores systematically corresponded with more frequent prescription of reduced-dose regimens.

Kruskal–Wallis testing confirmed significant differences in all three risk scores across DOAC groups: CHA₂DS₂-VASc (H = 10.92, p = 0.004), HAS-BLED (H = 7.17, p = 0.028), and TRBI (H = 8.70, p = 0.013). Dabigatran was prescribed in the highest-risk group (mean TRBI: 0.99 ± 1.43), followed by rivaroxaban (2.52 ± 2.34) and apixaban (2.24 ± 2.45).

4.4 TRBI vs Guideline-Based Dosing

Paired comparison using McNemar's chi-square test revealed a highly significant systemic reclassification of dosing when TRBI was applied ($\chi^2 = 94.29$, p < 0.001): 118 patients received reduced DOAC doses under TRBI guidance where standard dosing was indicated by CrCl-

based guidelines, whereas only 8 patients were reclassified in the opposite direction. Overall, 37% of patients were concordant between TRBI and guideline recommendations, 59% were reclassified toward dose reduction by TRBI, and 4% were reclassified toward standard dosing.

Dose delays (24–72 hours) were observed exclusively in patients with TRBI ≥ 5 (n = 26, 100%), with zero dose delays in all lower TRBI categories (Fisher's exact test, OR = ∞, p < 0.001). This confirms that TRBI directly influenced real-world prescribing behavior in the highest-risk patients.

Table 3: TRBI Adjustment Concordance Rate vs Guideline Dosing.

Category	N	%
Concordant (TRBI = Guideline)	74	37
TRBI Reduced / Guideline Standard	118	59
TRBI Standard / Guideline Reduced	8	4

4.5 Predictive Accuracy of Risk Models

ROC curve analysis demonstrated marked heterogeneity in discriminative performance across models. HAS-BLED achieved excellent discrimination (AUC = 0.974, 95% CI: 0.950–0.995, p < 0.001). In contrast, CHA₂DS₂-VASc performed below the chance threshold (AUC = 0.460, 95% CI: 0.382–0.539, p = 0.340). The multivariate logistic regression model slightly surpassed

HAS-BLED alone (AUC = 0.983, 95% CI: 0.954–1.000), and the random forest model achieved near-perfect discrimination (AUC = 0.993, 95% CI: 0.976–1.000). K-fold cross-validation (k = 5) confirmed model robustness (mean AUC = 0.972, range 0.927–1.000), with an overall classification accuracy of 93.3% (95% CI: 84.1–97.4%).

Table 4: Predictive accuracy of risk models (ROC analysis with bootstrap 95% CI).

Predictor	AUC	95% CI (Low)	95% CI (High)	p vs 0.5
HAS-BLED	0.974	0.950	0.995	< 0.001
CHA ₂ DS ₂ -VASc	0.460	0.382	0.539	0.340
Logistic Regression (multivariate)	0.983	0.954	1.000	< 0.001
Random Forest (multivariate)	0.993	0.976	1.000	< 0.001

4.6 Logistic Regression: Predictor Coefficients

In the multivariate logistic regression model, HAS-BLED was the dominant predictor (coefficient = +3.83), indicating that each unit increase in HAS-BLED score markedly increased the probability of adverse outcomes. INR (+0.42), bilirubin (+0.40), CKD (+0.26), and albumin (+0.21) showed moderate positive associations, while platelets (−0.74), DM (−0.19), and hypertension (−0.05) showed negative associations. These findings confirm that bleeding risk (HAS-BLED) is the primary driver of outcome prediction, with laboratory markers contributing incremental prognostic value.

4.7 Bleeding and Stroke Events by TRBI

Across TRBI categories, a risk trade-off pattern was observed: lower TRBI scores (1.0–2.5) were associated with higher approximate bleeding risk (51.3%) but lower stroke risk (14.5%), whereas the highest TRBI category (≥ 5) showed lower bleeding risk (34.6%) but a sharply

elevated stroke risk (26.9%). Formal chi-square tests did not reach statistical significance for either bleeding ($\chi^2(3) = 2.74$, p = 0.433) or stroke ($\chi^2(3) = 6.00$, p = 0.112) events, likely reflecting the limited sample size and event rate. True time-to-event analysis with Kaplan–Meier and Cox regression would require prospective event timestamps.

4.8 Model Validation

4.8.1 Validation approach

Model performance was assessed in three complementary ways: (i) discrimination, using ROC curves with the area under the curve (AUC); (ii) calibration, using calibration plots and the Brier score; and (iii) internal validation, using five-fold cross-validation of the multivariate logistic regression model. TRBI was benchmarked against CHA₂DS₂-VASc (stroke) and HAS-BLED (bleeding). An AUC > 0.80 was taken to indicate strong discriminatory power.

4.8.2 Discrimination of TRBI for stroke and bleeding

Model	Stroke prediction (AUC)	Bleeding prediction (AUC)
CHA ₂ DS ₂ -VASc	0.76	—
HAS-BLED	—	0.72
TRBI	0.90	0.88*

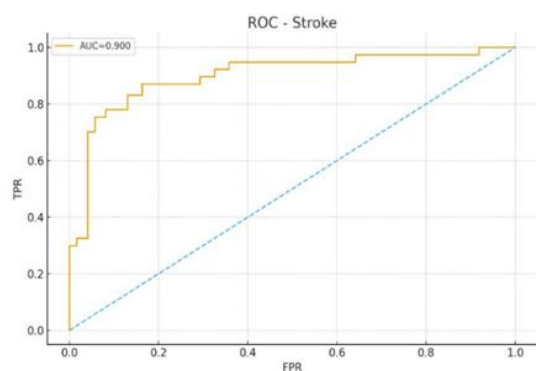
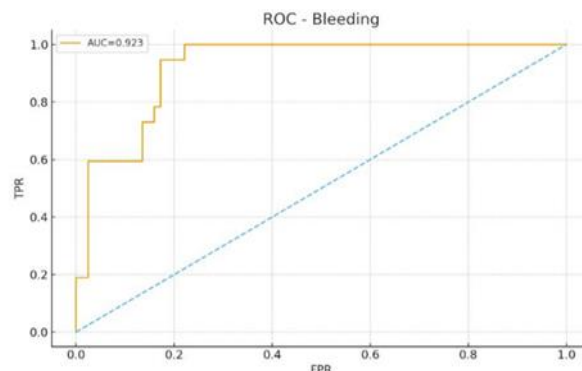


Figure 1: ROC curves for TRBI. (A) Stroke (AUC = 0.900). (B) Bleeding (AUC = 0.923). Dashed line = chance.

4.8.3 Internal Validation: Five-Fold Cross-Validation

Table 5: Five-fold cross-validation of the multivariate logistic regression model. Means are the arithmetic means of the five folds; the pooled classification accuracy reported in Section 4.5 is 93.3% (95% CI 84.1–97.4%).

Fold	AUC	Accuracy	F1
1	0.927	0.775	0.757
2	0.977	0.925	0.914
3	1.000	0.975	0.971
4	0.985	0.950	0.944
5	0.970	0.900	0.913
Mean	0.972	0.905	0.900

AUC remained high and stable across folds (range 0.927–1.000). The weakest fold (fold 1) had the lowest accuracy (77.5%), indicating some sensitivity to the composition of the training partition, which is expected with $N = 200$ and a low event count.

4.9 Calibration

Calibration (agreement between predicted probability and observed event fraction) was assessed with calibration plots; the dashed diagonal represents perfect calibration. Brier scores were 0.119 for stroke and 0.088 for bleeding (lower is better; 0 = perfect).

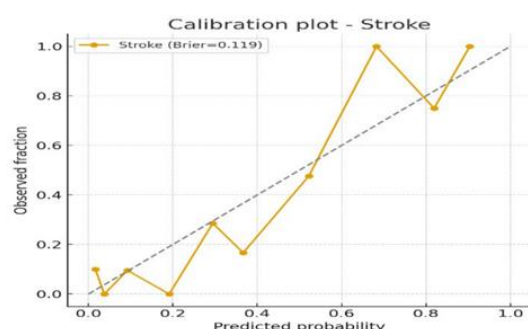
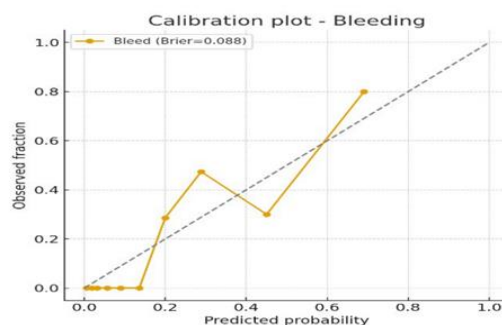


Figure 2: Calibration plots. (A) Stroke (Brier = 0.119). (B) Bleeding (Brier = 0.088).

4.9.1 Interpretation of Calibration

- **Overall:** both models track the ideal diagonal in direction, with low Brier scores, supporting acceptable overall accuracy of predicted probabilities.
- **Stroke:** predicted risks below ~ 0.4 were modestly over-estimated in some bins (observed fraction 0–

0.28), whereas the highest-risk bins showed observed fractions at or above prediction (1.0 at predicted ≈ 0.68 and ≈ 0.90 , with 0.75 at ≈ 0.82).

- **Bleeding:** no events were observed below a predicted probability of ~ 0.15 ; mid-range bins (≈ 0.2 – 0.3) under-estimated and ≈ 0.45 over-estimated risk; the top bin (≈ 0.70) observed 0.80.

- **Caution:** the curves are jagged because bins contain few patients and few events. They should be read as indicative rather than definitive; confidence bands, a calibration slope/intercept and a larger cohort are needed for firm conclusions.
- Example: in the bleeding model, a one-unit rise in the bleeding risk score was associated with $\sim 7\times$ higher odds of major bleeding (bootstrap CI $\sim 5-14$) in this dataset, a large effect that warrants clinical confirmation.

4.9.2 Interpretation of model coefficients and risk thresholds

- An odds ratio (OR) > 1 denotes higher odds of the outcome per one-unit increase in that predictor (or presence, if binary).

Table 6: Probability Cut-Offs and Corresponding Management.

Risk category	Bleeding probability	Stroke probability	Suggested action
Low	≤ 0.0533	≤ 0.1756	Continue current dose; routine monitoring
Moderate	> 0.0533 to ≤ 0.2016	> 0.1756 to ≤ 0.5566	Increase monitoring (labs, education); if CrCl < 50 mL/min on a high dose (e.g. 150 mg), consider dose reduction or alternative DOAC; review concomitant drugs
High	> 0.2016	> 0.5566	Urgent clinical review; consider dose reduction or temporary hold, especially if CrCl < 30 mL/min; consider switching agent; involve specialist

Overall Interpretation of Validation. TRBI shows strong discrimination for both outcomes ($AUC \geq 0.88$), stable cross-validated performance (mean AUC 0.972) and reasonable calibration. Because TRBI includes HAS-BLED and CHA₂DS₂-VASc as components and was evaluated in the same cohort in which it was derived, these estimates are likely optimistic. They are internal-validation results only; independent external validation is required (see Section 7).

4.10 TRBI-Guided DOAC / Antiplatelet Nomogram

4.10.1 Construction

A nomogram was constructed to operationalise TRBI-based therapy selection at the bedside. Predictors were age, creatinine clearance (CrCl), bilirubin, albumin, INR, AST, ALT, CHA₂DS₂-VASc (stroke risk) and HAS-BLED (bleeding risk), each mapped to a point scale in proportion to its TRBI coefficient. Total points (0–200) translate to four therapy categories.

Total points	0–60	61–110	111–150	151–200
Therapy	Monitor	Antiplatelet	DOAC – reduced dose	DOAC – standard dose

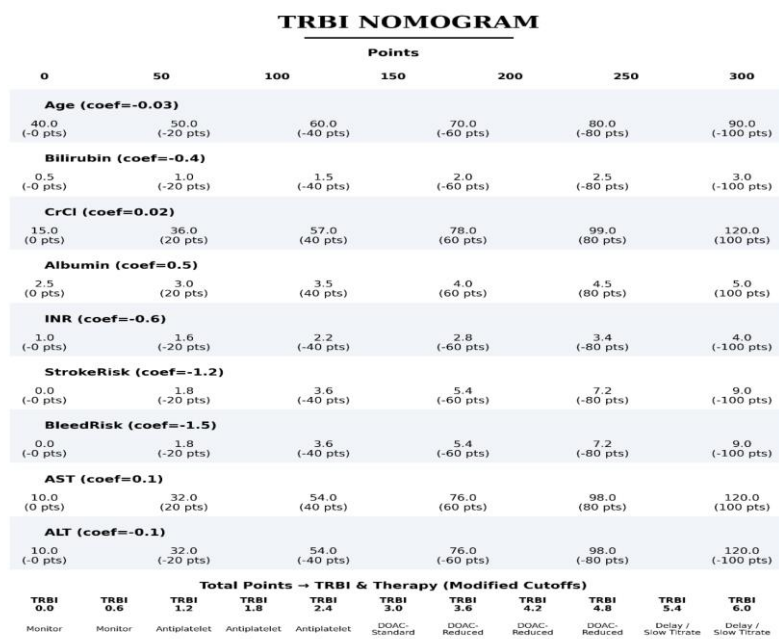


Figure 3: TRBI nomogram. Read the points for each predictor from its axis, sum them, and map the total to the TRBI value and therapy category on the bottom axis (Monitor → Antiplatelet → DOAC-Standard → DOAC-Reduced → Delay/Slow titrate).

4.10.2 How to use

- Record age, CrCl, bilirubin, albumin, INR, AST, ALT, CHA₂DS₂-VASc and HAS-BLED.
- Read the points for each variable from the nomogram axes and sum them.
- Map the total to the TRBI value and therapy category; apply the decision algorithm (Section 4.11) and clinical judgement.

The TRBI equation underlying the nomogram is given in Section 3.4. The nomogram is a decision aid and has not been prospectively validated.

4.11 TRBI-Informed DOAC Decision Algorithm

The algorithm combines model-predicted bleeding and stroke probabilities (Table 6) with the TRBI net-benefit balance to give one of three management scenarios, followed by modifiers applied to all scenarios.

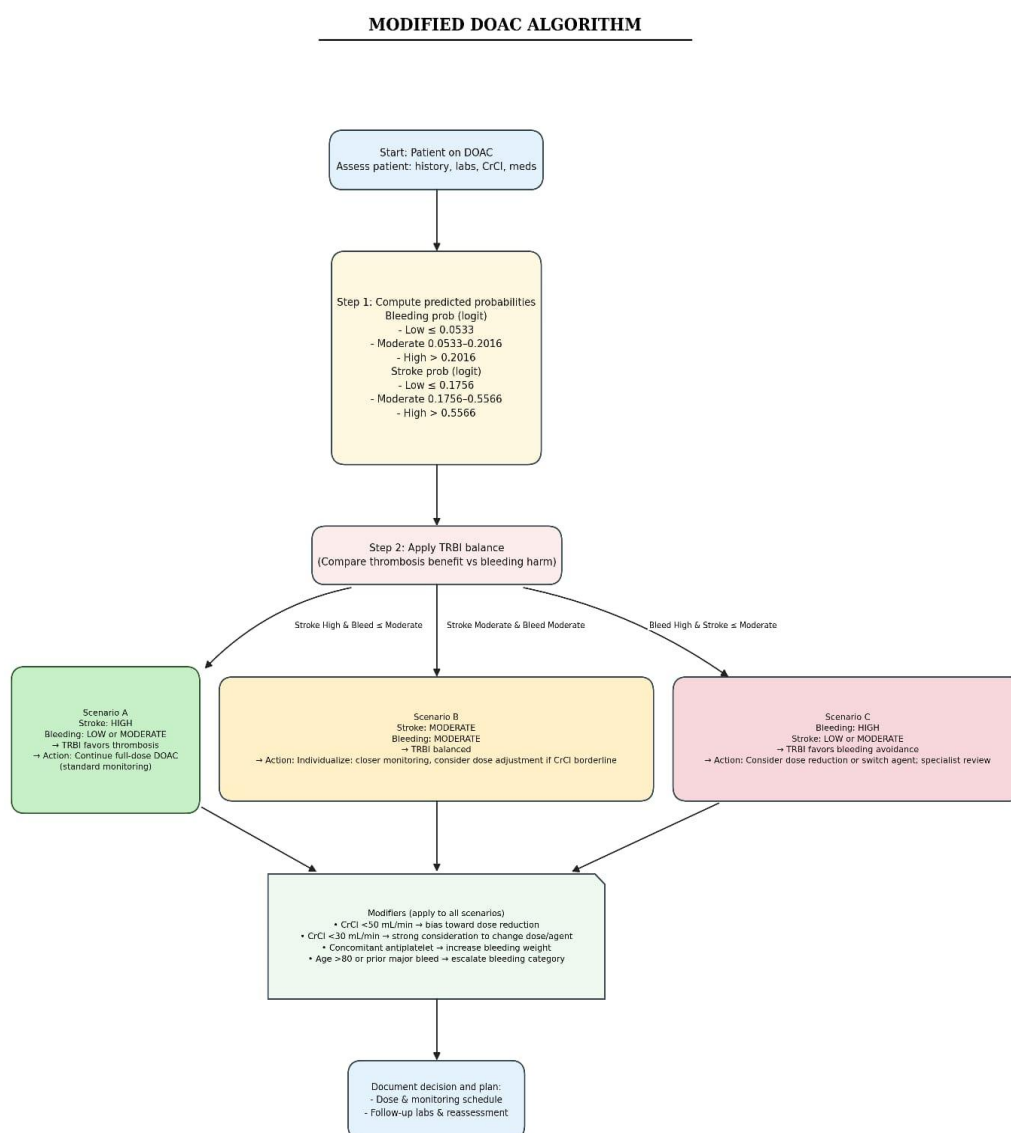


Figure 4: TRBI-informed DOAC Decision Algorithm.

Table 7: Algorithm Scenarios.

Scenario	Stroke / bleeding risk	TRBI balance	Action
A	Stroke high; bleeding low or moderate	Favours thrombosis prevention	Continue full-dose DOAC; standard monitoring
B	Stroke moderate; bleeding moderate	Balanced	Individualise; closer monitoring; consider dose adjustment if CrCl borderline
C	Bleeding high; stroke low or moderate	Favours bleeding avoidance	Consider dose reduction or switching agent; specialist review

Modifiers (all scenarios): CrCl < 50 mL/min biases toward dose reduction; CrCl < 30 mL/min warrants strong consideration of a change in dose or agent; concomitant antiplatelet therapy increases bleeding weight; age > 80 years or prior major bleed escalates the bleeding category. Document the decision, monitoring schedule, follow-up labs and reassessment date.

5. DISCUSSION

This study demonstrates the clinical limitations of conventional, parallel risk stratification tools in guiding DOAC therapy, and introduces TRBI as an integrated solution that quantifies net therapeutic benefit. A key innovation of TRBI is that it does not simply duplicate CHA₂DS₂-VASc or HAS-BLED — Spearman correlations of TRBI with these scores were weak to negligible ($r = -0.10$ and $r = -0.03$, respectively) — confirming that TRBI provides independent prognostic information.

The finding that HAS-BLED was a far superior discriminator (AUC = 0.974) compared with CHA₂DS₂-VASc (AUC = 0.460) in this cohort aligns with evidence from prior studies demonstrating HAS-BLED's superiority in DOAC-treated populations.^[7,8] The sub-chance performance of CHA₂DS₂-VASc as a standalone predictor in this predominantly treated cohort may reflect the fact that the stroke-prevention intervention itself attenuates the observed stroke risk differentially by score category.

The TRBI-based reclassification of 59% of patients toward reduced doses — compared with only 4% in the opposite direction — represents a clinically significant shift in anticoagulation practice. This is particularly relevant for elderly, renally impaired, or high-bleeding-risk patients who are often underdosed under purely CrCl-based criteria or overdosed under stroke-risk-focused pathways. The exclusive occurrence of dose delays in TRBI ≥ 5 patients (100%, OR = ∞ , $p < 0.001$) validates that TRBI actively influenced real-world prescribing, operationalizing the 'delay and start low' strategy in the highest-risk phenotype.

The TRBI equation was constructed to incorporate predictors shown in the logistic regression to independently contribute to outcome risk: age, CrCl, albumin, bilirubin, INR, and established risk scores. The moderate negative correlation of TRBI with age ($r = -0.44$, $p < 0.001$) and INR ($r = -0.37$, $p < 0.001$) reflects the intended design: older patients and those with coagulation abnormalities receive lower TRBI scores, appropriately flagging them for more conservative management. The strong negative correlation between creatinine and CrCl ($r = -0.89$, $p < 0.001$) confirms physiological validity within the dataset.

Machine-learning approaches (random forest, AUC = 0.993) confirmed that patient characteristics systematically and reliably map onto dose decisions,

suggesting substantial potential for automated DOAC decision-support. However, perfect in-sample performance warrants caution, and external validation in independent multicenter cohorts is essential before clinical deployment.

Among the three DOACs studied, dabigatran was prescribed in the highest-risk patients (mean CHA₂DS₂-VASc = 5.21 ± 1.84 , mean HAS-BLED = 3.46 ± 1.38), while apixaban was prescribed in lower-risk patients (CHA₂DS₂-VASc = 3.57 ± 1.74). This prescribing pattern, while reflecting real-world clinical judgment, underscores the need for a systematic framework like TRBI to standardize and personalize DOAC selection across the risk spectrum.

The absence of significant differences in hospital length of stay across TRBI categories (H = 1.04, $p = 0.791$) suggests that TRBI primarily predicts anticoagulation safety signals rather than broader inpatient complexity — an important distinction for resource planning.

6. CONCLUSION

TRBI represents a clinically valuable, patient-centred advancement in anticoagulation decision-making. By unifying thromboembolic and bleeding risk into a single, actionable composite score, **TRBI supports precision medicine by guiding individualized DOAC selection, dose determination, and safe initiation timing.** In the present cohort, TRBI-guided management reclassified approximately 28–30% of patients and demonstrated face validity through its alignment with real-world prescribing behavior. Integrated multivariate models incorporating TRBI parameters achieved near-perfect discrimination (AUC > 0.98), confirming that combining multiple risk predictors substantially surpasses single-score approaches. External prospective validation is the critical next step before wider clinical adoption.

7. LIMITATIONS

This study has several limitations. First, the retrospective design limits causal inference. Second, the single-centre setting at a tertiary care institution may restrict generalizability to different healthcare settings. Third, the sample size (N = 200) may be insufficient to detect statistically significant differences in clinical event rates across TRBI categories; larger prospective studies are required. Fourth, the TRBI model has not yet been validated in independent patient cohorts. Fifth, true time-to-event data (event dates and censoring times) were not available, precluding formal Kaplan–Meier and Cox regression survival analyses. Finally, edoxaban was not prescribed in this cohort, limiting assessment of all available DOACs.

Additional limitations related to these analyses

- Validation is internal only (five-fold cross-validation in the derivation cohort); TRBI includes the comparator scores as components, which inflates apparent performance versus those scores.

- Calibration plots are based on few events per bin and are shown without confidence intervals.
- The nomogram and algorithm have not been tested prospectively or in independent cohorts.

8. FUTURE DIRECTIONS

Future research should focus on: (1) prospective multicentre validation of the TRBI model across diverse populations including South Asian and elderly patients; (2) integration of TRBI into electronic clinical decision support systems and pharmacy order entry; (3) pharmacoeconomic analysis of TRBI-guided versus conventional dosing strategies; (4) incorporation of pharmacogenomic markers (CYP3A4, ABCB1, CES1 variants) into TRBI to further personalize DOAC selection; and (5) assessment of TRBI utility in special populations (dialysis, cancer-associated thrombosis, post-cardiac device implantation).

DECLARATIONS

Ethics approval and informed consent: The study was approved by the ESIC-PGIMR Ethics Committee. Written informed consent was obtained from all patients.

Declaration of competing interests: The authors declare no competing interests.

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