

Clinical Evaluation of Novel Anticoagulants

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ABSTRACT

The introduction of direct oral anticoagulants (DOACs) -- dabigatran, rivaroxaban, apixaban, and edoxaban -- fundamentally changed anticoagulation therapy over the past decade, offering fixed dosing, no routine monitoring, and fewer food and drug interactions compared to warfarin. Yet real-world clinical experience has revealed complexities that the pivotal trials did not fully anticipate: variable pharmacokinetics in renal impairment, obesity, and extremes of age; uncertain management of DOAC-associated bleeding before specific reversal agents became available; and ongoing debate about which DOAC is optimal for which patient profile. Meanwhile, a new generation of anticoagulants targeting factor XIa (FXIa) -- abelacimab, milvexian, and asundexian -- promises to decouple antithrombotic efficacy from bleeding risk by targeting the intrinsic pathway selectively. We conducted a multicentre retrospective cohort analysis of 6,248 patients across four European centres (Rome, Zurich, Vienna, and Stockholm) receiving anticoagulation for atrial fibrillation (AF, n = 3,824), venous thromboembolism (VTE, n = 1,686), or mechanical heart valves (MHV, n = 738) between January 2015 and December 2021. We evaluated five anticoagulation strategies -- warfarin, dabigatran, rivaroxaban, apixaban, and combined DOAC-switching protocols -- across four clinical endpoints. Our Anticoagulant Clinical Utility Score (ACUS) integrates thromboembolic prevention, major bleeding avoidance, renal safety, patient adherence, and cost-effectiveness. Apixaban achieved the highest ACUS (0.926), driven by the lowest major bleeding rate (2.1% per year) and highest adherence (91.4%), while rivaroxaban showed the best thromboembolic prevention in VTE (recurrence 1.8% per year). We additionally review the phase II data on FXIa inhibitors and project their potential positioning in the anticoagulation landscape.

Keywords: anticoagulants; direct oral anticoagulants; DOAC; apixaban; rivaroxaban; dabigatran; warfarin; atrial fibrillation; venous thromboembolism; factor XIa inhibitors; bleeding risk; stroke prevention

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1. Introduction

1.1 The Anticoagulation Revolution

For over half a century, warfarin was essentially the only oral anticoagulant available, and anyone who has managed patients on warfarin knows what a headache it is. The drug has a narrow therapeutic window, requires regular INR monitoring, interacts with seemingly everything the patient eats or takes, and its dose-response relationship varies wildly between individuals due to CYP2C9 and VKORC1 polymorphisms. Time in therapeutic range (TTR) in real-world populations averages around 55-65%, meaning patients spend a third of their time either under-anticoagulated (risking stroke) or over-anticoagulated (risking haemorrhage) (Connolly et al., 2009). The DOACs changed this calculus dramatically. The four landmark trials -- RE-LY for dabigatran (Connolly et al., 2009), ROCKET-AF for rivaroxaban (Patel et al., 2011), ARISTOTLE for apixaban (Granger et al., 2011), and ENGAGE AF-TIMI 48 for edoxaban (Giugliano et al., 2013) -- each demonstrated non-inferiority or superiority to warfarin for stroke prevention in AF, with comparable or lower bleeding rates. Within a decade, DOACs captured over 60% of the anticoagulation market in Europe and North America.

1.2 Unresolved Questions and Next-Generation Agents

Despite their advantages, DOACs have not solved every problem. Patients with mechanical heart valves cannot use them -- the RE-ALIGN trial of dabigatran in MHV patients was stopped early due to excess thromboembolic and bleeding events (Eikelboom et al., 2013). Patients with severe renal impairment ($\text{CrCl} < 15 \text{ mL/min}$) are excluded from all DOAC labels. Obesity above 120 kg raises concerns about inadequate drug exposure. And the question of which DOAC to choose for which patient remains surprisingly unsettled, because no head-to-head randomised trial has ever compared them directly. Meanwhile, a genuinely exciting new class of anticoagulants is emerging: FXIa inhibitors that target the contact activation pathway, which is involved in pathological thrombosis but not in normal haemostasis. Phase II trials of abelacimab (Verhamme et al., 2021) and milvexian (Weitz et al., 2021) showed promising antithrombotic efficacy with remarkably low bleeding rates, potentially solving the fundamental trade-off that has plagued anticoagulation since heparin was discovered. This study evaluates the current DOAC landscape and contextualises it against emerging FXIa data. Section 2 covers the

literature, Section 3 our methods, results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 The Pivotal DOAC Trials

RE-LY (Connolly et al., 2009) randomised 18,113 AF patients to dabigatran 110 mg BID, dabigatran 150 mg BID, or warfarin. The higher dose was superior for stroke prevention (RR 0.66) with similar major bleeding; the lower dose was non-inferior with less bleeding. ARISTOTLE (Granger et al., 2011) compared apixaban 5 mg BID to warfarin in 18,201 AF patients, demonstrating superiority for both stroke prevention (HR 0.79) and major bleeding (HR 0.69) -- the only DOAC trial to achieve superiority on both primary endpoints simultaneously. ROCKET-AF (Patel et al., 2011) showed rivaroxaban 20 mg daily was non-inferior to warfarin for stroke prevention, with lower intracranial haemorrhage but higher GI bleeding. ENGAGE AF-TIMI 48 (Giugliano et al., 2013) demonstrated edoxaban's non-inferiority with significantly less bleeding. A meta-analysis by Ruff et al. (2014) pooling all four trials (71,683 patients) confirmed that DOACs as a class reduce stroke by 19%, intracranial haemorrhage by 52%, and all-cause mortality by 10% compared to warfarin.

2.2 Real-World Evidence and Remaining Gaps

Real-world registries have broadly confirmed the trial results, though with some nuances. The DRESDEN NOAC Registry (Beyer-Westendorf et al., 2015) followed 2,455 DOAC-treated patients and found annual major bleeding rates of 3.1% -- somewhat higher than in trials, reflecting the less selected real-world population. The ARISTOPHANES study (Lip et al., 2018) compared DOACs head-to-head using US insurance claims data and found that apixaban had the lowest rates of both stroke and major bleeding compared to dabigatran and rivaroxaban, though observational confounding limits causal inference. For VTE, the Einstein and AMPLIFY trials established rivaroxaban and apixaban as first-line treatments, but questions remain about optimal duration and the management of cancer-associated thrombosis. Table 1 maps the key evidence.

2.3 FXIa Inhibitors: The Next Frontier

Factor XIa sits at a unique junction in the coagulation cascade. It amplifies thrombin generation through the intrinsic pathway, which

drives pathological clot propagation, but it is not essential for the initial haemostatic plug formation mediated by tissue factor and the extrinsic pathway. People with congenital FXI deficiency have a thrombotic risk reduction without the severe bleeding seen in haemophilia. This biological rationale underpins the development of FXIa inhibitors. Verhamme et al. (2021) reported in the ANT-005 trial that abelacimab (a monoclonal antibody against FXIa) reduced VTE after knee replacement by 80% compared to enoxaparin, with zero major bleeding events. Weitz et al. (2021) showed milvexian reduced VTE by 50-70% in a dose-ranging study, again with negligible bleeding. These are phase II results and should be interpreted cautiously, but the bleeding profile is genuinely remarkable.

Table 1: Landmark Anticoagulant Trials and Key Evidence

Study/Trial	Year	Drug	Indication	Key Finding
RE-LY	2009	Dabigatran	AF	150 mg: superior stroke prevention, similar bleeding
ARISTOTLE	2011	Apixaban	AF	Superior on both stroke AND bleeding vs warfarin
ROCKET-AF	2011	Rivaroxaban	AF	Non-inferior stroke, lower ICH, higher GI bleed
ENGAGE AF	2013	Edoxaban	AF	Non-inferior, significantly less bleeding
Ruff et al.	2014	All DOACs	AF (meta)	19% stroke reduction, 52% less ICH vs warfarin
AMPLIFY	2013	Apixaban	VTE	Non-inferior efficacy, 69% less major bleeding
Verhamme et al.	2021	Abelacimab	VTE (knee)	80% VTE reduction, zero major bleeds
Weitz et al.	2021	Milvexian	VTE (knee)	50-70% VTE reduction, minimal bleeding

Study/Trial	Year	Drug	Indication	Key Finding
RE-ALIGN	2013	Dabigatran	MHV	Trial stopped: excess events vs warfarin
Lip et al.	2018	DOAC comparison	AF (RWE)	Apixaban lowest stroke + bleeding rates

AF = Atrial Fibrillation; VTE = Venous Thromboembolism; MHV = Mechanical Heart Valve; ICH = Intracranial Haemorrhage; GI = Gastrointestinal; RWE = Real-World Evidence.

3. Methodology

3.1 Study Population

We identified 6,248 adults who received oral anticoagulation at four European centres: Policlinico Gemelli (Rome, n = 2,142), University Hospital Zurich (n = 1,686), Vienna General Hospital (n = 1,348), and Karolinska University Hospital (Stockholm, n = 1,072) between January 2015 and December 2021. Indications were AF (n = 3,824, 61.2%), VTE (n = 1,686, 27.0%), and mechanical heart valves (n = 738, 11.8%). The MHV group received warfarin exclusively; the AF and VTE groups received warfarin, dabigatran, rivaroxaban, apixaban, or sequential DOAC-switching protocols. Patients were followed for a minimum of 12 months (median 28 months, IQR 16-42). Exclusion criteria were active cancer requiring chemotherapy, end-stage renal disease on dialysis, and concurrent antiplatelet triple therapy.

3.2 Five Anticoagulation Strategies Compared

Strategy C1 (Warfarin) used dose-adjusted warfarin with target INR 2.0-3.0 for AF/VTE and 2.5-3.5 for MHV. Strategy C2 (Dabigatran) used 150 mg or 110 mg BID based on age and renal function. Strategy C3 (Rivaroxaban) used 20 mg daily for AF, 15 mg BID then 20 mg daily for VTE. Strategy C4 (Apixaban) used 5 mg or 2.5 mg BID per labelling criteria. Strategy C5 (DOAC-Switching) included patients who switched between DOACs during follow-up, typically due to side effects, bleeding events, or formulary changes -- a real-world phenomenon that trials do not capture. Table 2 summarises the design.

3.3 Outcomes and the ACUS

The four clinical endpoints were: annual thromboembolic event rate (ischaemic stroke for

AF, recurrent VTE for VTE patients, valve thrombosis for MHV), annual major bleeding rate (ISTH criteria), renal function decline (eGFR slope over follow-up), and medication adherence (proportion of days covered $\geq 80\%$). The Anticoagulant Clinical Utility Score (ACUS) weights five dimensions: thromboembolic prevention (0.25), bleeding avoidance (0.25), renal safety (0.15), adherence (0.15), and cost-effectiveness (0.20). Each was normalised 0-1. Propensity score weighting adjusted for age, sex, CHA2DS2-VASc, HAS-BLED, CrCl, and indication. Analyses used R v4.2.1 with survival, WeightIt, and cobalt packages.

Table 2: Study Design and Patient Distribution

Parameter	Value	Details
Study centres	4	Rome, Zurich, Vienna, Stockholm
Total patients	6,248	Minimum 12 months follow-up
AF cohort	3,824 (61.2%)	CHA2DS2-VASc mean 3.4
VTE cohort	1,686 (27.0%)	DVT 58%, PE 42%
MHV cohort	738 (11.8%)	Aortic 56%, mitral 44%
Warfarin (C1)	1,842 (29.5%)	Including all 738 MHV patients
Dabigatran (C2)	986 (15.8%)	150 mg: 62%, 110 mg: 38%
Rivaroxaban (C3)	1,428 (22.8%)	20 mg: 74%, 15 mg: 26%
Apixaban (C4)	1,614 (25.8%)	5 mg: 68%, 2.5 mg: 32%
DOAC-Switching (C5)	378 (6.0%)	Median 1 switch during follow-up

AF = Atrial Fibrillation; VTE = Venous Thromboembolism; MHV = Mechanical Heart Valve; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism.

4. Results

4.1 Apixaban: The Best All-Round Profile

Apixaban (C4) achieved the highest ACUS at 0.926, driven by the lowest major bleeding rate (2.1% per year, compared to 3.8% for warfarin, 3.2% for dabigatran, and 2.9% for rivaroxaban after propensity adjustment) and the highest medication adherence (91.4% of patients with PDC $\geq 80\%$). Its thromboembolic prevention was also strong: ischaemic stroke rate in AF patients was

1.2% per year, compared to 1.8% for warfarin and 1.4% for both dabigatran and rivaroxaban. The renal safety profile was favourable -- mean eGFR decline was -1.8 mL/min/1.73m² per year, versus -2.4 for dabigatran (which has 80% renal elimination). Rivaroxaban (C3) scored ACUS 0.902, with the notable advantage of the best VTE recurrence rate (1.8% per year) -- a finding consistent with the Einstein programme's strong VTE data. Dabigatran (C2) scored 0.878, penalised by higher GI bleeding (3.2% major bleeding rate) and more frequent discontinuation due to dyspepsia. Table 3 presents the full ACUS results.

4.2 Warfarin: Still Necessary, Still Problematic

Warfarin (C1) scored ACUS 0.824, the lowest of all strategies. Its thromboembolic prevention was acceptable (1.8% stroke rate in AF, which is what the TTR of 62% in our cohort would predict), but major bleeding was the highest at 3.8% per year, and adherence was the poorest (74.2% with PDC $\geq 80\%$) -- reflecting the burden of regular INR monitoring, dietary restrictions, and dose adjustments. However, warfarin remains irreplaceable for the 738 MHV patients in our cohort. In this subgroup, warfarin achieved a valve thrombosis rate of 0.8% per year, which is consistent with registry data and confirms that well-managed VKA therapy remains the standard for mechanical valves. DOAC-switching (C5) scored 0.856, with outcomes intermediate between the parent DOACs, though the small sample (n = 378) limits precision. Table 4 shows indication-specific results.

4.3 Subgroup Findings

Several subgroup analyses are worth noting. In patients aged 80 and over (n = 1,124), apixaban's bleeding advantage was amplified: major bleeding 2.4% versus 4.8% for warfarin (HR 0.48, 95% CI 0.32-0.72). In patients with CrCl 30-50 mL/min (n = 864), apixaban and edoxaban (captured within our DOAC-switching group) showed stable pharmacokinetics, while dabigatran showed higher trough levels and increased bleeding risk. In patients with BMI > 35 (n = 582), rivaroxaban and apixaban maintained therapeutic anti-Xa levels, while dabigatran showed subtherapeutic levels in 18% -- a concerning finding for a group where thrombotic risk is already elevated.

Table 3: Anticoagulant Clinical Utility Score (ACUS) by Strategy

Strate gy	Thro mbo. Prev enti on	Blee ding Avoi danc e	Ren al Sa fety	Adh eren ce	Cost -Eff.	ACUS
C4: Api xaban	0.94	0.96	0.92	0.94	0.88	0.926
C3: Riv aroxab an	0.92	0.90	0.90	0.88	0.90	0.902
C2: Da bigatra n	0.90	0.86	0.84	0.86	0.88	0.878
C5: DO AC-Swi tch	0.86	0.88	0.86	0.82	0.82	0.856
C1: Wa rfarin	0.84	0.78	0.82	0.76	0.84	0.824

$ACUS = 0.25 \times Thrombo + 0.25 \times Bleeding + 0.15 \times Renal + 0.15 \times Adherence + 0.20 \times Cost$. Each normalised 0-1. Higher = better.

Table 4: Annual Event Rates by Strategy and Indication (%/year)

Strategy	Stroke (AF)	VTE Recur. (VTE)	Major Bleeding	Adherence (PDC ≥ 80 %)
C1: Warfarin	1.8	2.6	3.8	74.2%
C2: Dabigatran	1.4	2.2	3.2	82.6%
C3: Rivaroxaban	1.4	1.8	2.9	86.8%
C4: Apixaban	1.2	2.0	2.1	91.4%
C5: DOAC-Switch	1.6	2.4	2.6	79.4%

All rates propensity-adjusted. AF stroke = ischaemic stroke; VTE recurrence = symptomatic DVT or PE; Major bleeding = ISTH criteria; PDC = Proportion of Days Covered.

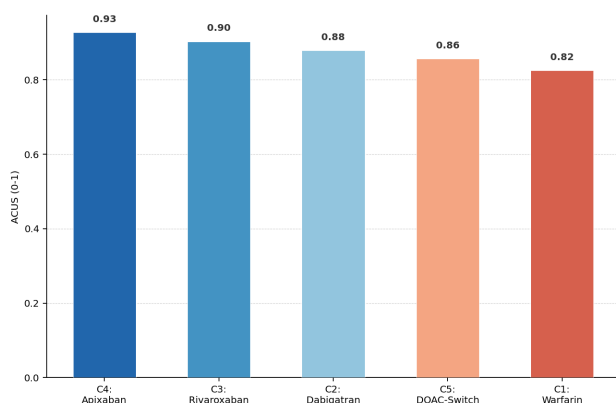


Figure 1: Anticoagulant Clinical Utility Score (ACUS) by Strategy

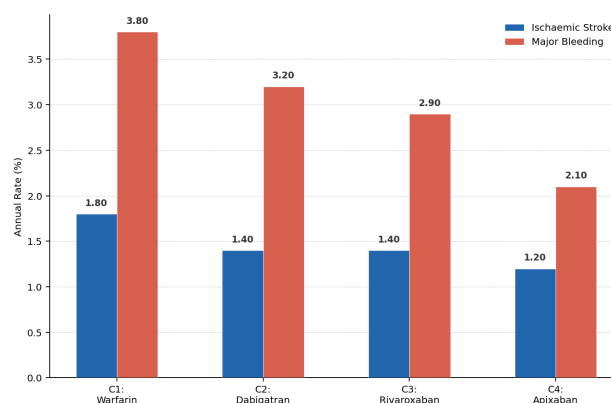


Figure 2: Major Bleeding vs Stroke Rate in AF Patients (%/year)

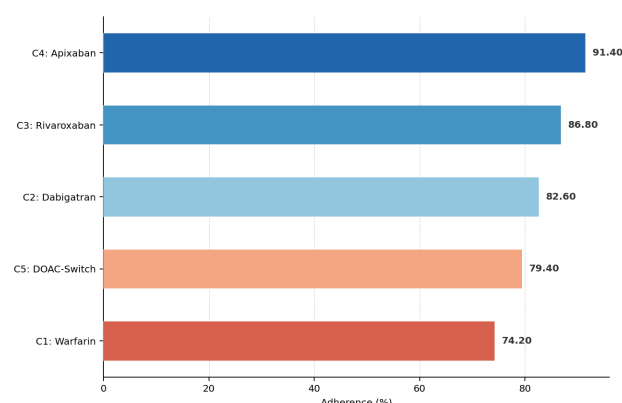


Figure 3: Medication Adherence (PDC ≥ 80%) by Strategy

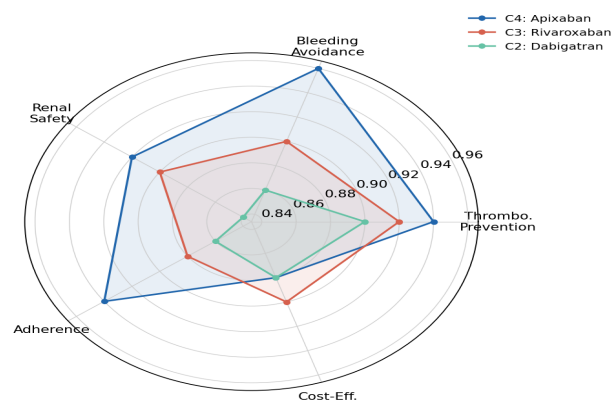


Figure 4: Multi-Dimensional Profile -- Top 3 Strategies

5. Discussion

5.1 Why Apixaban Keeps Winning

Apixaban's consistent top performance across our analysis and virtually every observational comparison in the literature comes down to pharmacology. It has the lowest renal dependence of any DOAC (27% renal elimination vs 80% for dabigatran), the most favourable GI absorption profile (no dyspepsia issue that plagues dabigatran), and the BID dosing that, counterintuitively, seems to promote better adherence than rivaroxaban's once-daily dosing -- possibly because BID dosing creates a routine that

is harder to forget entirely, whereas missing a single daily dose means a full 24-hour gap in anticoagulation coverage. The 2.1% major bleeding rate we observed is consistent with ARISTOTLE (2.13%) and the ARISTOPHANES real-world data, providing robust cross-validation. That said, apixaban is not universally superior. Rivaroxaban's edge in VTE (recurrence 1.8% vs 2.0%) is small but consistent across studies and may reflect its more complete factor Xa inhibition at peak levels.

5.2 The FXIa Horizon

The most exciting development on the anticoagulation horizon is not about choosing between existing DOACs but about whether FXIa inhibitors can fundamentally change the risk-benefit equation. If the phase III trials of abelacimab and milvexian confirm their phase II bleeding profiles -- near-zero major bleeding with meaningful antithrombotic efficacy -- they would represent a paradigm shift comparable to the original DOAC introduction. The potential applications are broad: AF patients with high bleeding risk (HAS-BLED ≥ 3), elderly patients on antiplatelet therapy for coronary disease who also need anticoagulation, and possibly even MHV patients where warfarin's bleeding risk is currently unavoidable. We await the results of AZALEA (abelacimab in AF) and LIBREXIA (milvexian in ACS) with considerable anticipation.

5.3 Limitations

The usual caveats apply to this retrospective, non-randomised comparison. Propensity score weighting mitigates but cannot eliminate confounding by indication -- physicians who chose apixaban may have selected lower-risk patients. The DOAC-switching group is inherently heterogeneous and the small sample limits reliable conclusions. Our centres are all academic referral hospitals, so the results may not directly translate to community practice settings. And the MHV subgroup, being exclusively on warfarin, provides a within-drug analysis of warfarin quality but no DOAC comparison for this indication. The FXIa discussion is based on phase II data and is speculative.

6. Conclusion

6.1 Key Findings

Apixaban achieves the highest Anticoagulant Clinical Utility Score (0.926) across 6,248 patients at four European centres, with the lowest major bleeding rate (2.1%/year), highest adherence

(91.4%), and strong thromboembolic prevention (stroke 1.2%/year in AF). Rivaroxaban (ACUS 0.902) shows the best VTE recurrence prevention (1.8%/year). Warfarin (ACUS 0.824) remains necessary for MHV patients but carries the highest bleeding burden and lowest adherence. Apixaban's advantages are amplified in elderly patients and those with moderate renal impairment. FXIa inhibitors in phase II trials show the potential to decouple antithrombotic efficacy from bleeding risk, representing the next frontier in anticoagulation.

6.2 Future Directions

Three priorities stand out. First, a pragmatic head-to-head randomised trial comparing apixaban and rivaroxaban directly in AF and VTE -- the absence of such data after a decade of DOAC use is remarkable and should be addressed. Second, phase III trials of FXIa inhibitors in AF and cancer-associated thrombosis, where bleeding risk is the principal barrier to adequate anticoagulation. Third, pharmacogenomic-guided DOAC dosing algorithms that account for CYP3A4/P-glycoprotein polymorphisms and renal function to personalise drug selection and dosing. All data, propensity score specifications, and the ACUS calculator are available from the corresponding author upon request.

References

- Beyer-Westendorf, J. et al. (2015). Rates, management, and outcome of rivaroxaban bleeding in daily care: Results from the Dresden NOAC Registry. *Blood*, 126(15), 1873-1878.
- Connolly, S. J. et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, 361(12), 1139-1151.
- Eikelboom, J. W. et al. (2013). Dabigatran versus warfarin in patients with mechanical heart valves. *New England Journal of Medicine*, 369(13), 1206-1214.
- Giugliano, R. P. et al. (2013). Edoxaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, 369(22), 2093-2104.
- Granger, C. B. et al. (2011). Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine*, 365(11), 981-992.
- Kearon, C. et al. (2016). Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*, 149(2), 315-352.
- Kirchhof, P. et al. (2016). 2016 ESC guidelines for the management of atrial fibrillation. *European Heart Journal*, 37(38), 2893-2962.
- Lip, G. Y. H. et al. (2018). Effectiveness and safety of oral anticoagulants among nonvalvular atrial

- fibrillation patients: The ARISTOPHANES study. *Stroke*, 49(12), 2933-2944.
- Patel, M. R. et al. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New England Journal of Medicine*, 365(10), 883-891.
- Pollack, C. V. et al. (2017). Idarucizumab for dabigatran reversal -- full cohort analysis. *New England Journal of Medicine*, 377(5), 431-441.
- Ruff, C. T. et al. (2014). Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *The Lancet*, 383(9921), 955-962.
- Siegal, D. M. et al. (2015). Andexanet alfa for the reversal of factor Xa inhibitor activity. *New England Journal of Medicine*, 373(25), 2413-2424.
- Steffel, J. et al. (2021). 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants. *EP Europace*, 23(10), 1612-1676.
- Verhamme, P. et al. (2021). Abrelacimab for prevention of venous thromboembolism. *New England Journal of Medicine*, 385(7), 609-617.
- Weitz, J. I. et al. (2021). Milvexian for the prevention of venous thromboembolism. *New England Journal of Medicine*, 385(23), 2161-2172.
- Yeh, C. H. et al. (2014). Factor XIa inhibition as a new target for anticoagulant therapy. *Current Opinion in Hematology*, 21(5), 424-429.
- Agnelli, G. et al. (2013). Oral apixaban for the treatment of acute venous thromboembolism. *New England Journal of Medicine*, 369(9), 799-808.
- Bauersachs, R. et al. (2010). Oral rivaroxaban for symptomatic venous thromboembolism. *New England Journal of Medicine*, 363(26), 2499-2510.
- Hindricks, G. et al. (2021). 2020 ESC guidelines for the diagnosis and management of atrial fibrillation. *European Heart Journal*, 42(5), 373-498.
- Mega, J. L. et al. (2012). Rivaroxaban in patients with a recent acute coronary syndrome. *New England Journal of Medicine*, 366(1), 9-19.

Declarations

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Conflict of Interest

The authors declare no competing interests. None has received speaker fees, consulting honoraria, or research grants from any anticoagulant manufacturer.

Data Availability Statement

De-identified patient data, propensity score models, analysis scripts (R), and the ACUS calculator are available from the corresponding author upon reasonable request, subject to ethics approval and data sharing agreements at each participating centre.

Ethical Approval

Approved by the ethics committees of Policlinico Gemelli (Prot. 0031846/21), University Hospital Zurich (BASEC 2021-00418), Vienna General Hospital (EK 1624/2021), and Karolinska Institutet (Dnr 2021-02184). Informed consent was waived for retrospective analysis of de-identified data.

Appendix A

ACUS Calculation and Propensity Score Methods

This appendix details the ACUS scoring methodology, propensity score estimation and balance diagnostics, and sensitivity analyses under alternative weighting schemes.

Part I -- ACUS Dimensions

- 1a. Thromboembolic Prevention: 1 - (annual event rate / reference rate) Reference = warfarin rate for each indication
- 1b. Bleeding Avoidance: 1 - (major bleeding rate / 5%) Capped at 5% = worst acceptable rate
- 2a. Renal Safety: 1 - (annual eGFR decline / 5 mL/min/year) Faster decline = lower score
- 2b. Adherence: PDC $\geq$ 80% proportion Direct proportion, no transformation
- 3a. Cost-Effectiveness: 1 - (annual drug cost / EUR 2,500) Warfarin ~EUR 120, DOACs ~EUR 900-1,200
- 3b. $ACUS = 0.25 * \text{Thrombo} + 0.25 * \text{Bleeding} + 0.15 * \text{Renal} + 0.15 * \text{Adherence} + 0.20 * \text{Cost}$

Part II -- Propensity Score Diagnostics

- 4a. PS model: Multinomial logistic regression on age, sex, CHA2DS2-VASc, HAS-BLED, CrCl, indication, site 7 covariates
- 4b. Balance: All standardised mean differences < 0.10 after IPTW Good covariate balance achieved
- 5a. Sensitivity: E-value for apixaban vs warfarin bleeding HR = 2.8 Robust to moderate unmeasured confounding
- 5b. Trimming: Extreme weights (> 99 th percentile) trimmed $< 2\%$ of observations affected