Personalized acute ischemic stroke management in the era of antithrombotic complexity: From risk stratification to reperfusion strategies

Doctoral (Ph.D.) Thesis

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1. Introduction

1.1. The burden of acute ischemic stroke

Acute ischemic stroke (AIS) is a leading cause of death and long-term disability worldwide. In Europe, it affects over one million people annually, a number expected to rise as populations age and vascular risk factors, such as atrial fibrillation (AF), hypertension, and diabetes mellitus, become more prevalent. Despite significant advances in both prevention and acute management, AIS continues to place a substantial burden on patients, their families, and healthcare systems. Many stroke survivors are left with lasting functional impairments, loss of independence, and reduced quality of life, often requiring prolonged rehabilitation and long-term care. These challenges underscore the ongoing need to strengthen both preventive and acute treatment strategies in stroke care.

Stroke is broadly defined as the sudden onset of focal neurological dysfunction resulting from disrupted cerebral blood flow, ultimately causing brain injury. AIS, which accounts for approximately 87% of all stroke cases, occurs when blood flow to the brain is blocked, depriving tissue of essential oxygen and nutrients, thereby triggering ischemic injury and subsequent infarction.

Etiologically, AIS can be classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into five major categories: cardioembolism, large artery atherosclerosis, small vessel occlusion (lacunar stroke), strokes due to other determined causes, and cryptogenic strokes. Each subtype presents distinct challenges related to prevention, diagnosis, and treatment, underscoring the importance of understanding the underlying mechanisms of stroke for optimal patient care.

1.2. Evolution and current state of acute ischemic stroke management

The introduction of intravenous thrombolysis (IVT) with alteplase in the mid-1990s represented a significant step forward, offering the first therapy proven to improve outcomes when administered within a limited time window after symptom onset. A second major breakthrough occurred in 2015, when multiple randomized controlled trials (RCTs) demonstrated the efficacy of mechanical thrombectomy (MT) for patients with large vessel occlusion (LVO) strokes. MT has since become the standard of care for eligible patients, significantly increasing the likelihood of functional independence.

1.3. The challenge of antithrombotic complexity in modern stroke care

As acute stroke therapies have evolved, the increasing use of antithrombotic agents, including antiplatelet agents, vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs), has added considerable complexity to the acute management of AIS. A growing number of patients now present with stroke while already receiving one or more of these medications, complicating clinical decision-making and risk assessment in the context of reperfusion therapy.

While all antithrombotic agents pose challenges in the hyperacute setting, the widespread adoption of DOACs, particularly among patients with AF, has had a defining impact. Favored over VKAs for their safety profile and ease of use, DOACs have largely replaced traditional anticoagulants. However, they have introduced a distinct set of diagnostic and therapeutic challenges that currently dominate much of the clinical debate in acute stroke care.

1.4. The clinical dilemma: Balancing benefit and risk

Clinicians are increasingly challenged to weigh the proven benefits of reperfusion therapies against the potential risks of hemorrhagic complications in anticoagulated patients. In routine practice, these decisions are often made on the basis of incomplete medication histories, limited access to rapid diagnostic testing, and uncertainty regarding the patient's actual anticoagulant activity at the time of presentation. As a result, patients receiving DOACs are frequently excluded from reperfusion therapy based on presumed, rather than objectively verified, bleeding risk.

2. Literature review

2.1. Guidelines and real-world practice: alignment and discrepancies

International guidelines for the acute management of AIS have evolved in parallel with advances in reperfusion therapies, offering increasingly refined recommendations regarding patient selection, imaging protocols, and therapeutic time windows. Both the European Stroke Organisation (ESO) and the American Heart Association/American Stroke Association (AHA/ASA) endorse IVT with alteplase within 4.5 hours of symptom onset, with selected cases eligible for treatment up to 9 hours after symptom onset. MT is recommended within 6 hours for LVO, with extensions to 24 hours in patients selected through advanced imaging criteria.

Despite significant advances in reperfusion therapy, managing AIS patients on prior antithrombotic treatment remains a clinical challenge. Current guidelines predominantly reflect expert consensus rather than robust randomized trial data. In patients on VKAs, IVT administration is deemed safe only if the international normalized ratio (INR) is below 1.7. In patients receiving DOAC therapy, IVT is generally contraindicated within 48 hours of the last dose (assuming a creatinine clearance ≥50 ml/min), unless anticoagulant activity can be reliably excluded through specific laboratory assays, such as diluted thrombin time (dTT) or ecarin chromogenic assay (ECA) for dabigatran, or calibrated anti-factor Xa assays for factor Xa inhibitors, or a reversal agent has been administered.

In contrast, MT guidelines do not formally exclude anticoagulated patients, they recommend individualized bleeding risk assessment and cautious clinical decision-making given the potential for hemorrhagic complications.

Large registries consistently show a gap between guideline recommendations and real-world clinical practice in the management of anticoagulated stroke patients: about one in six AIS patients presents on a DOAC, yet 80-90% of those arriving within the IVT window ultimately do not receive IVT. Emerging data challenge this restrictiveness: Seiffge *et al.* reported that IVT was safe in >50% of stroke patients taking rivaroxaban. However, under current guideline recommendations, approximately 28% of these patients would still be excluded, highlighting a disconnect between guideline-based exclusions and real-world eligibility.

At its core, the problem is that reported DOAC use does not reliably indicate active anticoagulation at presentation: up to 20% of patients who present with a stroke while reportedly taking a DOAC have no detectable anticoagulant activity on testing.

2.2. Residual stroke risk despite anticoagulation

Oral anticoagulant (OAC) therapy remains the cornerstone of stroke prevention in patients with non-valvular AF, reducing AIS risk by up to 64% compared to placebo. Both VKAs and DOACs were effective in large RCTs, with DOACs providing an additional 20% relative risk reduction and lower rates of symptomatic intracranial hemorrhage (sICH) compared to VKAs.

Despite these advances, a substantial proportion of patients still experience AIS while on OAC therapy. Across major RCTs, comparing DOACs with VKAs, annual AIS incidence ranged from 0.7-1.3% in primary prevention cohorts and 1.8-2.3% in secondary prevention populations. A recent pooled analysis further showed that AF patients already on OAC at their index stroke had a higher annual recurrence risk (8.9%) than anticoagulation-naive individuals, raising important questions about the mechanisms of therapeutic failure and implications for acute management.

2.3. The role of stroke subtype in prognosis and therapy response

Stroke subtype is a critical determinant of both recurrence risk and functional outcome following AIS, with direct implications for acute management decisions, including the use of reperfusion therapy.

Cardioembolic stroke (CES) is generally associated with greater initial stroke severity, larger infarct volumes, and higher recurrence risk, compared to other etiologies. In contrast, embolic stroke of undetermined source (ESUS), a subgroup of cryptogenic stroke, is defined by non-lacunar infarcts with a suspected embolic origin in the absence of a secondary cause, representing a heterogeneous clinical entity with distinct pathophysiological mechanisms. ESUS patients tend to be younger, experience less severe strokes, and have fewer cardiovascular comorbidities compared to patients with CES. In this context, recognizing subtype-specific patterns can be valuable when evaluating patients for reperfusion therapy.

2.4. Pre-stroke antithrombotic therapy and reperfusion safety

Building on the influence of stroke subtype and individualized risk stratification, another critical factor in acute reperfusion safety is the patient's pre-stroke antithrombotic therapy.

For patients on VKAs, the safety profile of IVT is generally reassuring, provided that the INR is ≤1.7 at presentation: sICH rates in this group are comparable to those in non-anticoagulated patients.

Although evidence on the safety of IVT in patients taking DOACs has historically been limited, recent registry-based analyses have helped refine our understanding of this topic. In one of the largest available cohorts (*n*=42,887) treated within 4.5 hours, those taking DOACs prior to stroke had comparable safety outcomes to other groups, though timing of last dose, admission coagulation parameters, and use of reversal agents were unavailable, limiting interpretation.

Clinical data indicate that IVT can be administered safely when DOAC-specific assays show low/undetectable plasma levels. A threshold of <30 ng/ml is commonly used across dabigatran, apixaban, and rivaroxaban, with sICH rates similar to non-anticoagulated patients. Small single-center series are reassuring even at higher anti-Xa levels: A single-centre study from Basel, Switzerland, treated 18 patients on rivaroxaban (three also underwent MT) using predefined anti-Xa cutoff values (<100 ng/ml), and reported no excess risk of sICH. A further single-centre study from Erlangen, Germany, applied similar predefined thresholds (<50 ng/ml or 50-100 ng/ml) across all four DOACs, treating 24 patients with IVT. Only one sICH occurred (4.2%), in a patient who also received MT. Consistently, Bücke *et al.* administered IVT at DOAC levels <100 ng/ml, and later, after a protocol change, also following individualized risk-benefit assessment irrespective of plasma level. Crucially, in the final IVT-treated group, the mean anti-Xa level was 41.7 ng/ml, and the median was 36.0 ng/ml (interquartile range [IQR] 18.0-60.0 ng/ml) which was substantially lower than in patients not treated with IVT (mean 108.5 ng/ml). Despite the broadened eligibility, sICH remained low (2.2%) and mortality did not increase. These findings challenge the need for rigid laboratory cutoffs for safe IVT, though data remain limited, and few patients with high DOAC levels were actually treated. Collectively, these studies support the potential safety of thrombolysis in carefully selected, anticoagulated patients, however, larger studies are needed to define safety margins at higher drug concentrations.

For MT, a recent meta-analysis demonstrated that patients on VKAs had a significantly higher risk of sICH following MT compared to non-anticoagulated controls (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.2-2.2). However, this elevated risk was not observed in patients receiving DOACs (OR 1.0, 95% CI 0.6-1.8). Moreover, DOAC-treated patients with LVO achieved notably higher recanalization rates (93.2%) compared to those on VKAs (81.5%) and controls without anticoagulation (84.2%), suggesting a potential procedural advantage in this subgroup.

2.5. Challenges in laboratory assessment of anticoagulant effect

One of the most significant obstacles to the safe and effective delivery of reperfusion therapies in anticoagulated AIS patients is the limitation of current laboratory diagnostics.

For patients on VKAs, the INR remains a well-established and accessible metric for guiding IVT eligibility. Nonetheless, as a cumulative marker, INR is influenced by recent dosing changes, dietary variations, hepatic function, and drug interactions, all of which may result in supratherapeutic INR values and increased bleeding risk.

Evaluating anticoagulant activity in patients on DOACs remains particularly challenging. Conventional coagulation assays, such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and by extension INR, have limited diagnostic accuracy for DOACs. Critically, routine coagulation tests demonstrate a poor correlation with actual DOAC plasma concentrations and anticoagulant effect, unlike VKAs, for which standard laboratory parameters reliably reflect the intensity of anticoagulation. Accurate evaluation of DOAC activity thus necessitates specialized assays, such as dTT or ECA for dabigatran, and calibrated anti-Xa assays for factor Xa inhibitors. However, these assays remain unavailable in many institutions, and their implementation has been primarily guided by expert consensus rather than standardized guideline recommendations.

2.6. Point-of-care-testing: A potential solution

In response to the diagnostic limitations outlined above, point-of-care testing (POCT) has emerged as a promising strategy for rapid, bedside evaluation of coagulation status in acute settings.

Viscoelastic POCT platforms, including rotational thromboelastometry (ROTEM®; Werfen, Barcelona, Spain), thromboelastography (TEG®; Haemonetics, Boston, Massachusetts, USA), and

the more recent ClotPro® (Haemonetics, Boston, Massachusetts, USA), offer whole-blood assays capable of detecting functional coagulation abnormalities in real-time.

While ROTEM® and TEG® have been widely adopted for perioperative and critical care settings, their available assays lack sensitivity for direct thrombin and factor Xa inhibitors, making them suboptimal for reliably ruling out clinically relevant anticoagulant effects in the acute stroke context.

In contrast, ClotPro® offers drug-specific assays that enable rapid assessment of anticoagulant activity. The ECA-test is designed for direct thrombin inhibitors such as dabigatran, with a commonly used clotting time (CT) threshold of <180 seconds corresponding to plasma concentrations below 50 or 100 ng/ml. For factor Xa inhibitors, including apixaban, rivaroxaban, and edoxaban, the Russell's viper venom (RVV)-test uses a CT of <100 seconds as the manufacturer-defined cutoff for minimal anticoagulant activity at both 50 and 100 ng/ml plasma concentrations. These targeted assays can deliver actionable results within minutes, making them particularly well-suited for time-sensitive decision-making in the emergency stroke setting.

2.7. Predictive models for personalized reperfusion decisions

Despite significant advances in acute stroke care, functional outcomes remain suboptimal for a considerable proportion of patients. Current evidence suggests that only 50-60% of patients eligible for IVT and 40-50% of those undergoing MT achieve functional independence (defined as a modified Rankin Scale [mRS] score of 0-2 at 90 days). Individual patient characteristics further influence clinical outcomes: advanced age and higher stroke severity at admission are consistently associated with poorer recovery trajectories.

In this context, accurately estimating functional outcomes following AIS is therefore central for informed clinical decision-making, particularly in anticoagulated patients, where the risks and benefits of reperfusion must be weighed rapidly and under considerable uncertainty. Over the past two decades, a range of prognostic models has been developed to support such decisions by providing early estimates of mortality risk, likelihood of functional independence, or the occurrence of major complications. Among the most widely adopted are the IScore, ASTRAL (Acute STroke Registry and Analysis of Lausanne), DRAGON (hypoDensity, pre-stroke mRS, Age, Glucose, Onset-to-treatment time, National Institutes of Health Stroke Scale [NIHSS]), and THRIVE (Totaled Health

Risks in Vascular Events) scores. These tools aim to generate clinically relevant risk estimates at the time of presentation, using variables typically available in the emergency setting.

The IScore, developed from a large Canadian stroke registry, incorporates factors such as age, sex, stroke subtype, stroke severity, comorbidities, pre-stroke functional status, and plasma glucose on admission. Although it demonstrates robust predictive value for 30-day and one-year mortality, its primary purpose lies in general outcome prognostication rather than in guiding real-time treatment decisions in the hyperacute phase. The ASTRAL score, in turn, uses variables such as age, baseline NIHSS, time from symptom onset to admission, level of consciousness, plasma glucose, and visual field assessment. While moderately accurate in predicting poor outcomes at three months, its practical application islimited by the availability and reliability of input variables in emergency settings, particularly when the time of onset is uncertain or patients are unable to communicate their clinical history. Notably, neither IScore nor ASTRAL incorporates treatment-related variables such as IVT or MT, despite these being strong determinants of clinical outcome in contemporary stroke care.

Other models, including DRAGON and THRIVE, were developed with a more focused therapeutic context. The DRAGON score is specific to patients treated with IVT, while THRIVE targets those undergoing MT. While effective within their intended populations, these models have limited generalizability across the broader AIS population.

Collectively, these models have contributed to more structured and objective risk assessment in AIS. Nonetheless, they are accompanied by significant limitations. To date, none of the established prognostic models have been developed or explicitly validated for anticoagulated stroke populations, despite the distinct risk profiles and clinical challenges this group presents. Many models rely on variables that are either unavailable or unreliable at the time of presentation, particularly in emergency contexts where information is incomplete. Moreover, few account for the influence of acute interventions, such as IVT or MT, which are now central to determining outcomes. As a result, their utility in guiding personalized treatment decisions during the hyperacute phase of care remains limited.

3. Aims

Although significant progress has been made in the treatment of AIS, managing patients who are already receiving antithrombotic therapy, particularly OACs, remains one of the most complex and debated challenges in clinical stroke care. The exclusion of this patient population from most major clinical trials has left important questions unanswered, particularly concerning the safety and effectiveness of reperfusion therapies in real-world settings. As a result, current practice often relies on incomplete medication histories, limited access to reliable coagulation testing, and a lack of individualized risk assessment tools. These factors contribute to inconsistent treatment decisions and the under-treatment of a growing group of patients.

This thesis aims to address these gaps by promoting more individualized and evidence-based decision-making in the acute management of anticoagulated stroke patients. Building on current clinical uncertainties, it explores both diagnostic and predictive strategies that could help clinicians make more accurate, timely, and patient-centered treatment decisions.

Specifically, this work aims to:

1. Investigate how pre-admission antithrombotic therapy, anticoagulation quality, and stroke etiology influence clinical outcomes and risk stratification in AIS.
2. Assess the clinical utility of point-of-care viscoelastic testing (ClotPro®) to detect active anticoagulant effect at admission and support safer reperfusion decisions.
3. Develop and internally validate a practical Stroke-SCORE to predict outcomes and guide personalized reperfusion planning in anticoagulated AIS patients.

4. Methods

To address these aims, this thesis draws upon seven original studies, each focused on a specific aspect of stroke care in anticoagulated patients. While the specific objectives and study populations vary, all analyses are built upon a consistent methodological framework.

4.1. Data sources

All analyses presented in this thesis are based on the Transzlációs Idegtudományi Nemzeti Laboratórium (TINL) STROKE-registry (RRF-2.3.1-21-2022-00011), an ongoing, prospective, single-center registry that captures all acute cerebrovascular admissions to the Department of Neurology at the University of Pécs, between February 2023 and May 2025. To ensure completeness data, registry entries were supplemented by a targeted retrospective review of clinical records from the Department of Emergency Medicine, University of Pécs. Data collection adhered to standardized institutional protocols and encompassed a diverse range of cases, reflecting the spectrum of stroke severity, comorbid conditions, and pre-stroke treatment patterns encountered in routine clinical practice.

4.2. Study populations

The primary study population included patients admitted with AIS, with or without prior antithrombotic therapy. Depending on the research question, analyses used either the full AIS cohort or predefined subcohorts stratified by antithrombotic status (DOAC, VKA, single antiplatelet therapy [SAPT] or dual antiplatelet therapy [DAPT], and antithrombotic-naïve individuals [reference cohort]) and by etiology (CES, ESUS, or cryptogenic). Where relevant, these etiologic subtypes were analyzed separately to assess heterogeneity in clinical outcomes and treatment-related risks.

4.3. Interventions

The therapeutic interventions investigated included IVT, MT, and their combination, all administered in accordance with current international guidelines and local institutional protocols. Decisions regarding reperfusion therapy were based on a comprehensive clinical assessment that incorporated a detailed medication history, standard laboratory parameters, and multimodal neuroimaging (computed tomography [CT], CT angiography, and magnetic resonance imaging [MRI]). In

selected studies, POCT with ClotPro® was additionally used to assess coagulation status in patients receiving DOACs, enabling real-time, individualized treatment decisions.

4.4. Assessment and outcomes

Outcomes were harmonized across studies to ensure consistency and enable meaningful comparisons. The primary efficacy endpoint was favorable 90-day outcome (mRS score of 0-2). Where available, functional trajectory was quantified using mRS-shift (pre-stroke mRS to 90 days). Safety endpoints were 90-day all-cause mortality (mRS score of 6) and intracranial hemorrhage, including sICH. Selected analyses also evaluated recurrent ischemic stroke and, among subtherapeutically anticoagulated patients treated with IVT, early neurological improvement (NIHSS-shift from baseline to 72 hours).

4.5. Statistical analysis

Baseline characteristics were summarized using frequencies (%) for categorical variables and as mean ± standard deviation (SD) or median (IQR) for continuous variables, as appropriate. Normality was assessed with the Shapiro-Wilk test. Group comparisons used χ^2 or Fisher's exact tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables (two groups). For comparisons across ≥3 groups, ANOVA or Kruskal-Wallis tests were applied as appropriate to the data distribution. Statistical significance was defined as a two-sided p-value of <0.05.

Confounding was addressed using 1:1 nearest-neighbor propensity score matching, Mahalanobis distance matching (± caliper), or inverse probability of treatment weighting (IPTW). Covariate balance was evaluated using standardized mean differences (SMDs), with thresholds of <0.10 indicating excellent balance and <0.20 indicating good balance.

Binary outcomes were modeled with multivariable logistic regression, ordered categorical outcomes with proportional-odds ordinal logistic regression, and change-from-baseline outcomes with linear regression. Models reported adjusted effect estimates (OR or β) with 95% CIs and were adjusted for clinically relevant covariates. Generalized additive models (GAMs) were used in selected analyses to capture non-linear predictor-outcome relationships. When outliers or model instability were present, we applied robust (Huber) or ridge regression with bootstrap resampling. To mitigate multicollinearity we performed principal component analysis (PCA) for dimensionality reduction.

The Stroke-SCORE was developed using gradient boosting (XGBoost) with hyperparameter tuning after triaging candidate predictors for clinical relevance, data completeness, and redundancy. Internal validation used k-fold cross-validation (with a train/test split as a sensitivity check). Discrimination was summarized by the area under the receiver operating characteristic curve (AUROC) with bootstrapped 95% CIs. Calibration was optimized with isotonic regression and evaluated using calibration plots and Brier scores, and model stability was assessed via bootstrap resampling.

All analyses were conducted in accordance with the STROBE guidelines. All data management, preprocessing, and analyses were performed using Python or R.

5. Results and Discussion

5.1. Reperfusion strategies and safety in anticoagulated patients

A persistent concern in anticoagulated patients with AIS is the presumed excess hemorrhagic risk of reperfusion therapy. To examine this risk under guideline-based selection, we analyzed our single-center registry (*"Trick or Treat(ment): Should We Still Fear Reperfusion Therapy in Anticoagulated Stroke Patients? —Comparable 90-Day Outcomes in a Propensity-Score-Matched Registry Study"*). Of 1,102 AIS admissions, 866 had complete data; 148 patients were receiving OACs (*n*=100 DOAC and *n*=48 VKA) and 718 were not. We created a balanced comparison using Mahalanobis-distance matching with a propensity-score caliper, yielding 126 well-matched pairs with excellent post-match balance.

After matching on key baseline variables (age, NIHSS score, pre-stroke mRS), outcomes were comparable between groups. Functional independence at 90 days (mRS ≤2) was achieved in 39.7% of anticoagulated patients and 45.2% of non-anticoagulated patients (p=0.445), no significant differences were observed in mortality or sICH. These results indicate that, among patients who meet contemporary safety criteria, pre-existing anticoagulation does not independently increase the risk of poor outcomes following reperfusion.

5.2. Stroke recurrence despite anticoagulation

The limitations observed in the acute management of anticoagulated stroke patients, particularly reliance on medication history rather than objective assessment, are also evident in the context of secondary prevention. While OACs are the cornerstone of stroke prevention in patients with AF, prescription alone does not ensure therapeutic protection. To examine why AIS still recurs "on OAC," we conducted the study *"Beyond Anticoagulation: Limitations of Oral Anticoagulants in Preventing Stroke Recurrence in Atrial Fibrillation,"* a retrospective analysis of 128 patients with AF and CES. Of these, 89 were receiving OAC at presentation (*n*=66 DOAC and *n*=23 VKA) and 39 were not. Within the OAC group, anticoagulation quality at presentation was classified as under-, appropriately, or over-anticoagulated (*n*=34, *n*=48, and *n*=7 patients, respectively), using INR thresholds for VKAs (under <2.0 and over >3.0 at admission) and label-concordant dosing for DOACs (under = off-label low dose and over = inappropriately high dose).

Using prior CES as a proxy for recurrence, crude rates were similar in OAC and non-OAC patients (19.1% vs 17.9%). However, the median interval between events was approximately twice as long among those on OAC (≈6 years vs ≈3 years), suggesting that anticoagulation delays rather than eliminates recurrence. Closer analysis revealed that residual risk was most strongly associated with suboptimal anticoagulation quality, driven by poor adherence, incorrect dosing, and pharmacokinetic interactions. When modeling the interaction between type and quality, the interaction was statistically significant (p=0.049), indicating that therapeutic anticoagulation, irrespective of whether achieved with a DOAC or a VKA, was associated with lower recurrence risk.

5.3. Stroke subtype and pre-admission antithrombotic therapy as outcome modifiers

Still focusing on embolic phenotypes, the study *"Shifting Outcomes: Superior Functional Recovery in Embolic Stroke of Undetermined Source Compared to Cardioembolic Stroke,"* compared recovery after ESUS versus CES. From 914 AIS admissions, 94 ESUS and 280 CES cases had 90-day mRS available. We performed 1:1 nearest-neighbor propensity-score matching (age, sex, pre-mRS, hypertension, diabetes, smoking, alcohol use, NIHSS score at admission and at 72 hours), yielding a balanced cohort of 188 patients (94 ESUS, 94 CES). Post-match balance was excellent (all SMDs <0.10) except for pre-mRS (0.26) and NIHSS score at 72 hours (0.33), which were retained as covariates in adjusted analyses.

After matching, ESUS patients were more likely to achieve functional independence at 90 days (mRS 0-2 in 69.1% vs. 44.7% for CES; Fisher's exact p=0.014; adjusted OR=3.35, 95% CI 1.28-8.78). Functional trajectory was also more favorable in ESUS, with a lower (better) adjusted mRS-shift (1.84 vs. 2.53; Mann-Whitney p=0.022). Thus, even after accounting for age, pre-stroke disability, and early neurological severity, subtype remained independently associated with recovery, supporting ESUS as a clinically distinct embolic phenotype. Clinically, these findings support an individualized approach to secondary prevention in ESUS while etiologic evaluation proceeds. Despite shared embolic features with CES, patients with ESUS remain without definitive secondary prevention guidelines, highlighting a significant gap in personalized management.

This uncertainty about optimal secondary prevention is not unique to ESUS; it is the defining challenge of cryptogenic stroke, where treatment decisions often precede a definitive etiologic diagnosis because the evaluation is incomplete, several mechanisms remain plausible, or no cause is iden-

tified despite appropriate testing. In this setting, secondary prevention commonly defaults to antiplatelet therapy (APT). Accordingly, in *"Pre-Admission Antiplatelet Therapy in Cryptogenic Stroke: A Double-Edged Sword,"* we examined whether arriving on APT already shapes early recovery. Of 224 cryptogenic AIS cases, 61 presented on APT (aspirin *n*=29, clopidogrel *n*=27, DAPT *n*=5). Using 1:1 nearest-neighbor propensity-score matching, we created 61 matched pairs (pre-APT vs no APT) and then fitted multivariable models that also accounted for time metrics and acute treatments.

Patients on prior APT were less likely to achieve functional independence at 90 days, this association persisted after matching and adjustment (adjusted OR for mRS 0-2 = 0.21, p=0.018). Consistently, model-based marginal predictions in the matched cohort showed lower independence probabilities with pre-admission APT, and the observed proportions in both the unmatched and matched samples mirrored this pattern. These observations align with the heterogeneity of cryptogenic stroke. Many cryptogenic presentations ultimately reveal an atrial source; thus, while APT is a pragmatic default under diagnostic uncertainty, it is inadequate when the true mechanism is cardioembolic. Because CES are typically more severe, poorer outcomes among patients on pre-admission APT likely reflect a mechanism-treatment mismatch rather than harm from APT itself. Moreover, pre-admission APT often signals higher baseline vascular risk (residual confounding by indication), and platelet inhibition in the setting of covert small-vessel disease may heighten susceptibility to microbleeds or hemorrhagic transformation, particularly with coexisting hypertension or diabetes, thereby attenuating functional recovery.

5.4. Point-of-care testing for individualized decision-making

Following our initial analyses, which showed that patients on OACs treated according to guideline recommendations had outcomes comparable to those not receiving anticoagulation, the study *"Putting DOAC Doubts to Bed(side): Preliminary Evidence of Comparable Functional Outcomes in Anticoagulated and Non-Anticoagulated Stroke Patients Using Point-of-Care ClotPro® Testing"* used point-of-care viscoelastic testing (ClotPro®) to confirm anticoagulant activity at the bedside. We then matched patients with confirmed DOAC intake to non-anticoagulated controls (1:1; *n*=36; 18 vs. 18) and compared 90-day outcomes after reperfusion therapy.

Among patients treated with IVT or MT per clinical protocols, those with confirmed anticoagulation achieved functional outcomes similar to non-anticoagulated patients with no significant increase in mortality or sICH. Importantly, clinical decision-making remained conservative: this study did not advocate unrestricted IVT in all anticoagulated patients. Rather, it extended the findings from the *"Trick or Treat(ment)"* study, where anticoagulation status was inferred from history, by objectively confirming DOAC effect at presentation. The results support that carefully selected anticoagulated patients can safely undergo reperfusion therapy when evaluated with appropriate point-of-care diagnostics.

Building on our previous work demonstrating that viscoelastic POCT (ClotPro®) can objectively confirm on-arrival anticoagulant activity, the next step was to address a clinically relevant question: among patients with self-reported DOAC intake, how many are in fact eligible for IVT at the time of presentation? Accordingly, the primary aim of the subsequent prospective proof-of-concept study *"Viscoelastic Point-of-Care Testing (ClotPro®) to Guide Intravenous Thrombolysis in Acute Ischemic Stroke Patients on DOACs: Replacing History with Hemostasis in a Proof-of-Concept Study"* was patient selection, i.e., to identify an IVT-eligible, subtherapeutic subgroup using bedside ClotPro® testing. Secondary aims were to compare early neurological improvement (NIHSS-shift), 90-day functional outcomes (mRS-shift), and safety (mortality, sICH) between subtherapeutic patients who did and did not receive IVT.

Of 147 DOAC-reported patients, 40 underwent POCT, 15/40 (37.5%) had no measurable anticoagulant effect (subtherapeutic) and were therefore potentially eligible for IVT, of whom 7 ultimately received IVT. To evaluate outcomes within this subgroup, we used propensity-score matching with bootstrap resampling (1,000 iterations) to compare IVT-treated patients with matched subtherapeutic controls. Early neurological improvement consistently favored IVT across most resamples (not statistically significant), while 90-day mRS-shift was similar between groups. Mortality appeared higher in the IVT group, however, all deaths occurred in patients who also underwent MT, suggesting confounding by baseline severity or procedural risk. Importantly, no sICH occurred (one hemorrhagic infarction type 2 on imaging), indicating that IVT was safe in carefully selected subtherapeutic patients. These findings show that POCT can move decision-making from history-based exclusion to hemostasis-based inclusion, thereby expanding safe access to IVT without an observed safety penalty.

5.5. Predictive models for personalized care

While POCT improves the accuracy of anticoagulation assessment in the acute setting, clinicians still need practical tools that convert routinely available data into clear bedside guidance. To address this gap, the study "*Stroke-SCORE: Personalizing Acute Ischemic Stroke Treatment to Improve Patient Outcomes*" derived and internally validated a simple prediction model.

The Stroke-SCORE uses only three variables available at presentation, age, admission NIHSS score, and pre-stroke mRS to generate a point-based estimate of the probability of 90-day functional independence (mRS ≤2) and classify patients into low-, moderate-, or high-risk categories. The model showed strong discrimination (AUROC 0.86) with balanced operating characteristics (sensitivity 79%, specificity 81%), supporting its clinical utility for identifying patients most likely to benefit from reperfusion therapy.

Designed for the hyperacute phase, the Stroke-SCORE relies only on routinely collected clinical data. Without requiring additional laboratory or imaging inputs, it enables early, structured estimation of functional prognosis in anticoagulated patients. By offering individualized risk stratification at the point of care, the model supports more nuanced and evidence-informed clinical decision-making.

6. Conclusions

This thesis offers a structured, evidence-based evaluation of reperfusion therapy in anticoagulated patients with AIS, and shows how care can improve through objective, time-critical assessment and individualized decision-making. Across complementary studies, it demonstrates that reliance on patient-reported medication histories and the absence of hyperacute, objective measures of anticoagulant effect can lead to overly conservative exclusions from reperfusion therapy for patients who might otherwise benefit.

In response, the work develops and evaluates an individualized decision framework that integrates POCT to verify clinically relevant anticoagulant activity, presentation-time predictive modeling based on routinely available data to estimate treatment benefit and hemorrhagic risk, and etiologic considerations when feasible. Collectively, these components align therapy with patient-specific risk profiles, broadening appropriate access to IVT and MT while maintaining, and in some contexts improving, safety and effectiveness.

Analyses demonstrate that a substantial subset of anticoagulated patients historically excluded under conservative criteria can safely achieve meaningful clinical benefit when selection is guided by objective, time-critical data. They also reveal marked heterogeneity across stroke subtypes and the practical implications of this diversity for both acute therapy and secondary prevention, challenging uniform protocols that do not account for etiologic variation.

Together, this work lays the foundation for transforming clinical practice toward a more nuanced precision-medicine approach, one that carefully balances ischemic and hemorrhagic risks, enhances individualized patient outcomes, and supports the evidence-based refinement of clinical guidelines. As such, it represents a significant advance in the care of a complex and growing patient population.

7. Scientometrics

Scientific papers: 10

Cumulative impact factor: 31.8 (Journal Citation Reports™, year of article acceptance)

Publications related to the present thesis (cumulative impact factor: 21.0)

1. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., & Szapáry, L. (2024). *Beyond Anticoagulation: Limitations of Oral Anticoagulants in Preventing Stroke Recurrence in Atrial Fibrillation*. **Journal of Clinical Medicine**, 13(23), 7309. https://doi.org/10.3390/jcm13237309
   Impact Factor (2023): 3.0 – Q1
2. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., & Szapáry, L. (2025). *Stroke-SCORE: Personalizing Acute Ischemic Stroke Treatment to Improve Patient Outcomes*. **Journal of Personalized Medicine**, 15(1), 18. https://doi.org/10.3390/jpm15010018
   Impact Factor (2023): 3.0 – Q1
3. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., & Szapáry, L. (2025). *Pre-Admission Antiplatelet Therapy in Cryptogenic Stroke: A Double-Edged Sword*. **Journal of Clinical Medicine**, 14(4), 1061. https://doi.org/10.3390/jcm14041061
   Impact Factor (2023): 3.0 – Q1
4. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., & Szapáry, L. (2025). *Shifting Outcomes: Superior Functional Recovery in Embolic Stroke of Undetermined Source Compared to Cardioembolic Stroke*. **Neurology International**, 17(3), 35. https://doi.org/10.3390/neurolint17030035
   Impact Factor (2023): 3.2 – Q2
5. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., Jozifek, E. J., & Szapáry, L. (2025). *Viscoelastic Point-of-Care Testing (ClotPro®) to Guide Intravenous Thrombolysis in Acute Ischemic Stroke Patients on DOACs: Replacing History with Hemostasis in a Proof-of-Concept Study*. **Neurology International**, 17(7), 103. https://doi.org/10.3390/neurolint17070103
   Impact Factor (2023): 3.0 – Q2
6. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., Jozifek, E. J., & Szapáry, L. (2025). *Putting DOAC Doubts to Bed(Side): Preliminary Evidence of Comparable Functional*

Outcomes in Anticoagulated and Non-Anticoagulated Stroke Patients Using Point-of-Care ClotPro® Testing. **Journal of Clinical Medicine**, 14(15), 5476. https://doi.org/10.3390/jcm14155476
Impact Factor (2023): 2.9 – Q1

7. **Seetge, J.,** Cséke, B., Karádi, Z. N., Bosnyák, E., Jozifek, E. J., & Szapáry, L. (2025). *Trick or Treat(ment): Should We Still Fear Reperfusion Therapy in Anticoagulated Stroke Patients?—Comparable 90-Day Outcomes in a Propensity-Score-Matched Registry Study.* **Journal of Clinical Medicine**, 14(22), 8146. https://doi.org/10.3390/jcm14228146
Impact Factor (2023): 2.9 – Q1

Other publications

8. **Seetge, J.**, Cséke, B., Karádi, Z. N., Bosnyák, E., & Szapáry, L. (2024). *Bridging the Gap: Improving Acute Ischemic Stroke Outcomes with Intravenous Thrombolysis Prior to Mechanical Thrombectomy*. **Neurology International**, 16(6), 1189–1202. https://doi.org/10.3390/neurolint16060090
Impact Factor (2023): 3.2 – Q2
9. **Seetge, J.**, Cséke, B., Karádi, Z. N., Szalai, E., Gaál, V., & Szapáry, L. (2025). *Subsequent Acute Ischemic Stroke in a Patient with Monocular Vision Loss Associated with Isolated Internal Carotid Artery Occlusion: A Case Report*. **Neurology International**, 17(1), 3. https://doi.org/10.3390/neurolint17010003
Impact Factor (2023): 3.2 – Q2
10. **Seetge, J.***, Frenger, J.*, Katan, M., Grosse, G. (2025). *Recent advances in stroke biomarkers – implications for prognosis and treatment.* **Current Opinion in Neurology**, 39(1), 17–25. https://doi.org/10.1097/wco.0000000000001450
Impact Factor (2023): 4.4 – Q1

Conferences

National Conferences

- Undergraduate Research Society (TDK) fall conference, 1st prize, 11/2023
- Undergraduate Research Society (TDK) fall conference, 2nd prize, 11/2024
- National Undergraduate Research Society (OTDK) conference, 1st prize, 04/2025
- Hungarian Stroke Society (MST) conference, 09/2025
- Hungarian Society on Thrombosis and Haemostasis (MTHT) conference, 10/2025

International Conferences

- Accepted poster presentation, European Stroke Organisation Conference (ESOC), Basel, Switzerland, 05/2024
- Accepted poster presentation, 14th International Conference on Neurological Disorders & Stroke, Zurich, Switzerland, 10/2024
- Accepted poster presentation, 7th Annual Conference of the ESC Council on Stroke, Athens, Greece, 11/2024
- Accepted poster presentation, 24th Kongress der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin (DIVI) e.V., Hamburg, Germany, 12/2024
- Accepted poster presentation, European Stroke Organisation Conference (ESOC), Helsinki, Finland, 05/2025
- Accepted poster presentation, Deutscher Schlaganfallkongress (DSG25), Berlin, Germany, 09/2025
- Accepted poster presentation, 8th Annual Conference of the ESC Council on Stroke, Milan, Italy, 11/2025

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