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MOLECULAR AND CLINICAL PREDICTORS OF COGNITIVE DECLINE AND STROKE IN ATRIAL FIBRILLATION: A MULTICENTER STUDY OF NOACs VS VKAs USING MACHINE LEARNING APPROACHES

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Abstract

Atrial fibrillation (AF) is increasingly recognized not only as the most common sustained arrhythmia in older adults, but also as a clinical syndrome capable of influencing long-term brain health. In recent years, the classical association between AF and ischemic stroke has been expanded by evidence linking AF to cognitive decline, mild cognitive impairment, and dementia even in patients with no history of clinically overt cerebrovascular events. This broader view implies that overt cardioembolism is only one component of the problem. Silent brain infarction, cerebral microbleeds, chronic cerebral hypoperfusion, endothelial dysfunction, systemic inflammation, multimorbidity, and the cumulative effects of long-term anticoagulation quality may all contribute to progressive neurocognitive injury. Within this context, the comparison between vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs) acquires clinical relevance beyond stroke prevention alone, because more stable anticoagulation and a lower burden of hemorrhagic complications may plausibly translate into superior cognitive preservation over time.

The present doctoral thesis was developed to investigate molecular and clinical predictors of cognitive decline in elderly patients with non-valvular AF and to evaluate whether the type of oral anticoagulant therapy is associated with different longitudinal cognitive trajectories. The work integrates two complementary components. The first is a multicenter cohort study focused on elderly outpatients with AF followed over time with serial cognitive assessment. The second is a mechanistic biomarker substudy performed in the subgroup of patients who developed ischemic stroke during follow-up, in whom acute thrombo-inflammatory and neuroglial markers were characterized. The conceptual core of the thesis lies in the integration of clinical reasoning with machine-learning methodology, under the hypothesis that cognitive decline in AF is not driven by a single dominant variable but by the interaction of multiple demographics, cardiovascular, metabolic, renal, hemodynamic, and laboratory factors.

The AF cohort included 983 elderly patients with newly diagnosed non-valvular AF enrolled in a multicenter observational setting. Baseline cognition was evaluated by Mini-Mental State Examination (MMSE), and longitudinal cognitive decline was defined as any reduction in MMSE score between baseline and follow-up reassessment. At baseline, the mean age was 76 ± 6 years, 49% of participants were male, hypertension was present in 86%, diabetes mellitus in 35%, and current smoking in 8%. Overall, 70% of the cohort received NOACs and 30% received VKAs. Baseline MMSE categories were normal cognition in 58%, borderline cognition in 18%, and mild cognitive impairment in 24%, without significant imbalance between the anticoagulant groups. In multivariable logistic regression, NOAC therapy was independently associated with lower odds of cognitive decline than VKA therapy (odds ratio 0.322; 95% confidence interval 0.221-0.469; $p < 0.0001$). A Random Forest classifier demonstrated robust predictive performance, with mean repeated stratified cross-validated ROC AUC of approximately 0.8715 (SD 0.0273). On the held-out test set, the class-weighted model achieved ROC AUC 0.880, whereas a SMOTE-based strategy improved recall for the decline class while maintaining acceptable overall discrimination. Predicted decline probabilities differed markedly between anticoagulant groups, and permutation importance identified anticoagulant therapy as the most influential predictor, followed by glycemia, systolic blood pressure, body mass index, albumin, and potassium.

The biomarker substudy included 116 patients with acute ischemic stroke and 59 controls. A panel including osteopontin (OPN), platelet factor 4 (PF4), interferon gamma-induced protein 10 (IP-10), soluble thrombomodulin (sCD141), ubiquitin C-terminal hydrolase L1 (UCH-L1), glial fibrillary acidic protein (GFAP), and fatty acid-binding protein 3 (FABP3) was explored using plasma assays. Significant between-group differences were documented for OPN, PF4, and UCH-L1, while the combined PF4+OPN+UCH-L1 model reached an AUC of 0.827. These molecular findings provide biological plausibility for the clinical

model, suggesting that event-related thrombo-inflammatory and neuroglial signatures may represent mechanistic links between AF, stroke, and subsequent cognitive deterioration.

Taken together, the present work supports three major conclusions. First, cognitive decline in AF is a multidimensional process in which arrhythmic burden, vascular risk, anticoagulation quality, and molecular injury pathways converge. Second, in this elderly multicenter population, NOAC therapy was associated with a substantially lower probability of cognitive decline than VKA treatment. Third, machine-learning approaches, particularly Random Forest, are well suited to capture heterogeneous and nonlinear clinical patterns that may be poorly represented by conventional models alone. These findings support a precision-medicine framework in AF, in which preservation of cognitive function becomes a central therapeutic objective and not merely a secondary consequence of stroke prevention.

List of Abbreviations

ABBREVIATION	DEFINITION
AAD	anti-arrhythmic drug
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
AF	atrial fibrillation
AIS	acute ischemic stroke
ALT	alanine aminotransferase
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CKD	chronic kidney disease

COI	cognitive impairment
COPD	chronic obstructive pulmonary disease
DOAC/NOAC	direct oral anticoagulant / non-vitamin K oral anticoagulant
ELISA	enzyme-linked immunosorbent assay
GFAP	glial fibrillary acidic protein
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs/alcohol
HOMA	homeostasis model assessment
IP-10	interferon gamma-induced protein 10
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
OAT	oral anticoagulant therapy
OPN	osteopontin
PF4	platelet factor 4
PR	precision-recall
RF	Random Forest
ROC	receiver operating characteristic
SMOTE	synthetic minority over-sampling technique
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UCH-L1	ubiquitin C-terminal hydrolase L1
VKA	vitamin K antagonist

1. Introduction

1.1 Epidemiology and clinical relevance of AF-related cognitive decline

Atrial fibrillation has become one of the clearest examples of how demographic transition reshapes cardiovascular medicine. As life expectancy increases and survival after myocardial infarction, heart failure, valve disease, and chronic metabolic disorders improves, the number of individuals living long enough to develop AF continues to rise [1-4]. Contemporary epidemiology therefore reflects two overlapping processes: true biological susceptibility linked to aging and comorbidity, and improved detection through wider use of ambulatory monitoring, implantable devices, and digital technologies [1-2]. The consequence is a rapidly expanding clinical population characterized not only by arrhythmia, but by multimorbidity, frailty, polypharmacy, and competing risks.

In practical terms, AF is no longer merely an electrophysiological diagnosis. It is a chronic condition that affects quality of life, hospitalization rates, functional decline, and survival. It also exhibits marked heterogeneity across sex, ethnicity, and healthcare systems [5-8]. Lifetime risk estimates from large cohort studies indicate that AF is likely to occur in approximately one out of three White adults over midlife, although this risk varies according to baseline cardiovascular burden and population characteristics [6-7]. Projections for Europe, North America, and Asia suggest a continued rise in prevalence over the next decades, implying a substantial increase in the number of elderly patients exposed to cardioembolic, hemorrhagic, renal, and neurocognitive complications [1-2].

The traditional clinical focus in AF has centered on stroke, heart failure decompensation, and rhythm or rate management. However, this perspective is now too narrow. AF should instead be understood as the clinical expression of a broader atrial cardiomyopathy, characterized by electrical remodeling, structural fibrosis, endothelial dysfunction,

neurohormonal activation, and systemic inflammation [3-4,9-10]. These mechanisms not only sustain the arrhythmia itself but may also influence cerebral perfusion, blood-brain barrier integrity, and vulnerability to covert cerebrovascular injury. For that reason, the long-term significance of AF increasingly extends beyond symptomatic arrhythmia or overt embolism.

The elderly population is the natural setting in which these processes become clinically most relevant. Older adults with AF accumulate multiple determinants of brain fragility: hypertension, diabetes, chronic kidney disease, small-vessel disease, sleep-disordered breathing, atherosclerosis, and reduced physiological reserve. Once these factors coexist, the question is no longer whether AF may influence cognitive health, but how strongly, through which pathways, and whether therapeutic choices can modify this trajectory. This perspective places cognitive decline at the center of AF care rather than at its periphery.

Cognitive impairment is itself a growing public-health challenge driven by the aging of the global population. Community-based studies show broad heterogeneity in the prevalence and incidence of cognitive impairment among adults over 50 years of age, partly because of differences in diagnostic thresholds, educational attainment, cultural context, and screening tools [11]. Even so, the overall direction is unambiguous: the absolute number of people living with mild cognitive impairment and dementia is rising steadily, and the burden on patients, caregivers, and healthcare systems is substantial.

The spectrum of cognitive decline ranges from subtle deficits detectable only on formal testing to advanced dementia with severe dependency. This continuum has important implications for studies in AF. First, many affected individuals are not yet frankly demented and may still preserve substantial functional autonomy. Second, cognitive trajectories are not uniform; they differ according to baseline reserve, vascular risk exposure, neurodegenerative substrate, and the occurrence of overt or covert cerebrovascular events. Third, small changes in cognition, when accumulated over years, can meaningfully influence

adherence, treatment complexity, fall risk, and the ability to recognize symptoms or comply with anticoagulant monitoring.

From an epidemiological standpoint, cognitive impairment cannot be interpreted as a purely neurological issue. Cardiovascular and cerebrovascular determinants contribute significantly to its incidence and progression. Hypertension, diabetes, obesity, dyslipidemia, renal dysfunction, and smoking all influence both vascular brain injury and neurodegenerative processes [11-13]. In elderly patients with AF, these shared risk factors create a clinical scenario in which the arrhythmia may amplify an already vulnerable brain milieu. Thus, studying cognition in AF does not mean examining an isolated outcome; it means analyzing the cumulative expression of chronic vascular injury, embolic risk, perfusion abnormalities, and systemic inflammatory stress over time.

Another important epidemiological point is that cognitive decline often precedes its own diagnosis. The interval between early memory complaints, measurable decline on structured tests, and clinically overt dementia may span years. This is especially relevant for longitudinal AF cohorts, where baseline cognitive screening provides an opportunity to identify subclinical vulnerability before disabling decline has become apparent. It also underscores the importance of repeated assessment, because a single cognitive time point may fail to capture the dynamic nature of deterioration. For these reasons, serial MMSE-based evaluation, while imperfect, remains a practical tool for large observational studies and allows clinically interpretable tracking of change over time [14-15].

The association between AF and cognitive impairment was initially interpreted through a straightforward causal chain: AF leads to cardioembolic stroke, and stroke leads to dementia. Although this pathway remains valid, it is now incomplete. Meta-analytic and longitudinal evidence has shown that AF is associated with cognitive decline and dementia even after accounting for prior stroke history [16-17]. This suggests that clinically overt

cerebrovascular events explain only a fraction of the neurocognitive burden attributable to AF.

Several observations support the concept of AF as an independent cognitive risk factor. First, stroke-free patients with AF may already exhibit poorer memory performance and structural brain abnormalities, including hippocampal atrophy, compared with individuals in sinus rhythm [18]. Second, serial neuroimaging studies have documented the occurrence of silent brain infarcts, white-matter injury, and microvascular abnormalities in anticoagulated AF populations [19-20]. Third, cognitive decline in AF has been reported across different age groups, but may be particularly relevant in younger-old patients, in whom the effect is less likely to be obscured by advanced frailty or established dementia [16-17].

AF may therefore be conceptualized as a state of chronic cerebrovascular vulnerability. The arrhythmia exposes the brain to intermittent embolic showering, hemodynamic instability, and systemic inflammatory activation. None of these factors needs to produce a dramatic neurological event in order to be clinically meaningful. A small, strategically located silent infarct, repetitive hypoperfusion of vulnerable watershed regions, or progressive damage to white-matter networks may each be sufficient to impair attention, executive function, processing speed, or memory over time. The end result can be gradual decline rather than sudden neurological catastrophe.

This framework has two major clinical implications. The first is that cognitive outcomes should be explicitly considered when choosing an anticoagulant strategy and during longitudinal management. The second is that prediction models limited to conventional stroke-risk scores are unlikely to capture the full architecture of neurocognitive risk. A patient may remain free from major stroke while still accumulating subclinical brain injury. Thus, the thesis focuses on cognitive decline as a primary longitudinal outcome and not merely as a post-stroke sequel.

1.2 Pathobiology of atrial fibrillation and mechanisms of the heart–brain axis

Atrial fibrillation arises from the interaction of focal triggers, a permissive atrial substrate, and multiple modulators including autonomic tone, inflammation, and neurohormonal stress. Ectopic activity originating from the pulmonary veins remains one of the classic initiating mechanisms, but sustained AF generally requires more than isolated triggers [9-10,21]. Structural remodeling of the atrial myocardium, characterized by fibrosis, chamber dilation, altered connexin expression, and conduction heterogeneity, creates the substrate in which re-entry circuits can be maintained. Electrical remodeling further shortens atrial refractoriness and stabilizes the arrhythmia.

From a systems perspective, AF is closely related to the concept of atrial cardiomyopathy. Rather than being a purely electrical disorder, AF often reflects cumulative atrial injury caused by hypertension, diabetes, obesity, obstructive sleep apnea, valvular disease, inflammation, and age-related myocardial changes [3-4,9-10]. These determinants promote atrial stretch, endothelial activation, blood stasis, platelet activation, and thrombin generation. Once established, AF may in turn worsen atrial dysfunction and perpetuate a vicious circle in which "AF begets AF," while at the same time enhancing systemic thrombo-inflammatory signaling.

This broader pathobiological model matters for cognition because the same substrate that favors thrombogenesis also reflects generalized vascular and inflammatory dysfunction. A diseased atrium is not only a source of emboli; it is also a marker of chronic cardiovascular remodeling that may parallel or promote cerebral microvascular injury. In addition, irregular ventricular response and loss of coordinated atrial contraction can reduce cardiac output and impair beat-to-beat cerebral flow regulation, especially in older adults with reduced vascular reserve.

The relevance of atrial cardiomyopathy is therefore twofold. First, it offers a mechanistic explanation for why AF may affect the brain independently of clinically apparent stroke. Second, it supports the search for integrated predictive models that incorporate clinical and biochemical variables rather than rhythm classification alone. In the present thesis, the hypothesis is that anticoagulant class interacts with this underlying substrate and may influence the accumulation of neurovascular damage over time.

Cognition is not a single function but a set of interrelated domains including memory, attention, language, visuospatial ability, and executive control. Clinical impairment may selectively affect one domain or several, and the functional consequences depend not only on test scores but also on educational background, premorbid reserve, mood, sensory status, and coexisting medical illness. Contemporary nosology distinguishes mild neurocognitive disorder, often operationalized as mild cognitive impairment, from major neurocognitive disorder or dementia [15,22]. The distinction is clinically useful because it separates measurable decline that still allows independence from decline that compromises daily life.

In AF cohorts, this distinction has practical value. Many older adults do not present with advanced dementia but rather with subtle or borderline impairment that may influence medication adherence, appointment attendance, interpretation of symptoms, or understanding of anticoagulation risks. Accordingly, detecting early decline may carry therapeutic significance even before frank dementia develops. In real-world clinical practice, extensive neuropsychological batteries are not always feasible, especially in multicenter observational cohorts. The MMSE therefore remains attractive because it is brief, widely known, and easy to repeat longitudinally [14]. Although it is less sensitive for executive dysfunction than more specialized tools, it provides a pragmatic measure of global cognitive change.

The interpretation of MMSE change requires caution. Scores may be influenced by education, fatigue, sensory impairment, cultural context, and inter-rater variability.

Nevertheless, when serially applied within a structured follow-up design, changes in MMSE can still reflect clinically meaningful cognitive trajectories. In this thesis, cognitive decline was operationalized as any reduction in MMSE score between baseline and the second follow-up assessment. This choice intentionally privileges sensitivity to decline rather than restricting the analysis to advanced or categorical cognitive endpoints. It fits the central clinical question of the study: whether long-term anticoagulant strategy is associated with preservation or deterioration of cognition over time.

Another relevant point is that cognitive impairment in AF is not purely vascular and not purely neurodegenerative. Instead, it may result from the interaction of both. Small-vessel disease, silent infarcts, hypoperfusion, inflammation, and reduced reserve may lower the threshold at which Alzheimer-type or other neurodegenerative pathology becomes clinically manifest. The study of cognitive decline in AF therefore lies at the intersection of cardiology, internal medicine, vascular neurology, geriatrics, and translational biology.

The relationship between AF and cognitive decline is best understood through a heart-brain axis model in which several mechanisms act concurrently rather than sequentially [12,23-24]. Overt ischemic stroke remains the most visible component of this axis, but it is only one part of a much wider network of injury pathways.

A first mechanism is cerebral embolic injury, both overt and covert. AF promotes thrombus formation through atrial stasis, endothelial dysfunction, platelet activation, and hypercoagulability. While large emboli may cause disabling stroke, smaller embolic events can produce silent brain infarcts that are detectable only on MRI yet still correlate with cognitive decline [19-20]. These lesions often involve white matter, subcortical structures, or border-zone regions and may disrupt networks essential for executive function and processing speed. Because they remain clinically silent, their cumulative burden may be underestimated in routine care.

A second mechanism is cerebral microbleeding and hemorrhagic microangiopathy. Older patients with AF, especially those requiring long-term anticoagulation, may harbor cerebral microbleeds that represent a substrate of fragile cerebral small vessels [25]. These lesions are relevant not only because they increase hemorrhagic risk, but also because they indicate diffuse cerebral vascular pathology. In practical terms, the brain of an elderly anticoagulated AF patient may be exposed simultaneously to ischemic and hemorrhagic microinjury.

A third pathway is chronic cerebral hypoperfusion. AF abolishes coordinated atrial systole and creates irregular ventricular cycles, producing beat-to-beat variability in cerebral blood flow. In patients with impaired vascular autoregulation, this may reduce perfusion of vulnerable regions such as hippocampal and watershed territories. Over time, repeated episodes of relative hypoperfusion may contribute to synaptic dysfunction, white-matter damage, and reduced resilience to superimposed ischemic insults [18,24]. This mechanism is particularly attractive because it explains cognitive decline even in patients without imaging evidence of major embolic lesions.

A fourth component is systemic and neurovascular inflammation. AF has been associated with elevated inflammatory mediators, oxidative stress, endothelial activation, and a prothrombotic state [12,26]. These factors may alter blood-brain barrier permeability, amplify microglial activation, and favor a milieu in which vascular and neurodegenerative pathology reinforce each other. Inflammatory signaling may also interact with renal dysfunction, metabolic disease, and aging-related immune dysregulation, further increasing cerebral vulnerability.

Finally, comorbidity clustering magnifies all these pathways. Hypertension, diabetes, heart failure, chronic kidney disease, chronic lung disease, obesity, and sleep-disordered breathing are common in AF and independently associated with impaired cognition [11,13]. The heart-brain axis in AF is therefore not a simple one-directional phenomenon but a multidimensional system in which arrhythmia, vascular disease, organ dysfunction, and

inflammation converge. This complexity provides the rationale for a machine-learning approach capable of handling nonlinear interactions and mixed clinical data types.

1.3 Oral anticoagulation and cognitive preservation

Oral anticoagulation is the cornerstone of stroke prevention in AF and, from a pathophysiological standpoint, one of the most plausible interventions for preserving cognition. If recurrent overt or covert embolic injury contributes to neurocognitive decline, then reducing thromboembolic burden should protect the brain [27]. Yet the issue is more nuanced than simply anticoagulation versus no anticoagulation. The quality, stability, and safety profile of anticoagulation may all influence long-term cerebral outcomes.

Vitamin K antagonists are highly effective when maintained within an adequate therapeutic range, but real-world treatment is often characterized by INR variability, dietary and drug interactions, and periods of under- or over-anticoagulation. Subtherapeutic exposure may fail to prevent embolic injury, whereas supratherapeutic exposure may increase bleeding complications and potentially contribute to microhemorrhagic brain injury. These limitations are especially relevant in older adults, who often experience multimorbidity, fluctuating renal function, polypharmacy, and reduced adherence capacity.

NOACs offer a more predictable pharmacokinetic and pharmacodynamic profile, fixed dosing, fewer interactions, and a lower incidence of intracranial hemorrhage in several settings [28]. For that reason, they may provide a more stable long-term balance between ischemic protection and bleeding avoidance. The question is whether this advantage translates into better preservation of cognition. The literature remains mixed. Some cohort studies and meta-analyses suggest lower dementia risk in anticoagulated patients and possibly a benefit of DOACs/NOACs over warfarin, whereas other analyses emphasize the role of confounding and the importance of time in therapeutic range among VKA-treated patients [27-30].

Still, there are biologically plausible reasons why NOACs may be advantageous. More consistent anticoagulation may reduce silent infarct burden; lower intracranial bleeding risk may reduce cumulative hemorrhagic microinjury; and favorable vascular or renal effects observed in some studies may indirectly influence brain health [29-32]. In the context of elderly AF, these potential mechanisms are clinically meaningful because cognitive decline is a long-horizon outcome that may reflect many years of cumulative vascular injury. The present thesis therefore examines anticoagulant class not merely as a treatment variable but as a central determinant of longitudinal neurocognitive risk.

1.4 Machine learning and multidimensional prediction in atrial fibrillation

Traditional regression remains indispensable in clinical research because it yields interpretable estimates, supports causal reasoning, and allows direct adjustment for prespecified confounders. However, the prediction of cognitive decline in AF presents challenges that are not optimally addressed by linear models alone. The relevant predictor space is broad, heterogeneous, and potentially nonlinear. Demographics, comorbidities, hemodynamic variables, biochemical parameters, baseline cognition, and treatment choices may each contribute modestly, while interactions among them may be more informative than any isolated effect [33-36].

Machine learning is particularly attractive in this setting because it can accommodate complex feature structures without requiring the investigator to specify every possible interaction in advance. Ensemble tree methods such as Random Forest are robust to mixed data types, relatively resistant to overfitting when appropriately validated, and capable of ranking variables by predictive importance [35,37]. Moreover, Random Forest can capture threshold effects and nonlinear relationships that may be clinically realistic: for example, the impact of blood pressure, glycemia, kidney function, or age may not be constant across all patients.

Another key issue is class imbalance. In many longitudinal cohorts, the subgroup developing cognitive decline is smaller than the subgroup that remains stable. Standard classifiers may then be biased toward the majority class. Techniques such as class weighting and SMOTE can partially mitigate this problem by improving sensitivity to the minority outcome [38]. From a clinical perspective, this matters because a model that misses a large fraction of patients at risk may have limited practical utility even if its overall accuracy appears acceptable.

The adoption of machine learning should not be interpreted as a rejection of classical methods. In this thesis, multivariable logistic regression and Random Forest are viewed as complementary. Regression quantifies the independent association between NOAC use and cognitive decline, whereas machine learning explores how that treatment variable behaves within a higher-dimensional predictive ecosystem. This dual strategy aligns with current recommendations for responsible clinical prediction modeling, where discrimination, calibration, interpretability, and transparent reporting must all be considered [33].

Machine learning refers to a family of computational methods that learn predictive structure from data. In supervised learning, the algorithm is trained on examples for which the outcome is known and then applied to new observations. In clinical medicine, this usually means predicting an event, class, or probability from a set of patient-level variables. The apparent simplicity of the idea hides several methodological challenges: data quality, missingness, class imbalance, overfitting, transportability, and interpretability all influence the real value of a model [33-36].

Random Forest, the algorithm selected in the present study, is an ensemble method based on the aggregation of multiple decision trees [37]. Each tree is trained on a bootstrap sample of the data, and at each split the algorithm considers a random subset of predictors. The final prediction is obtained by combining the predictions of the individual trees. This process reduces variance relative to a single decision tree and makes the model more stable. It is

especially suited to structured clinical datasets in which predictor-outcome relationships are complex and possibly nonlinear.

Performance assessment in machine learning requires more than a single accuracy value. ROC AUC is widely used to describe overall discrimination, but in imbalanced datasets it should be interpreted alongside precision, recall, F1-score, and precision-recall AUC. A highly specific model may still perform poorly if it misses too many positive cases. Threshold choice therefore becomes clinically relevant. In prediction problems such as cognitive decline, one may prefer a threshold that increases sensitivity and identifies more vulnerable patients even at the cost of more false positives, depending on the intended use of the model.

Finally, feature importance measures help clinicians understand which variables most strongly influence model performance. These measures do not establish causality, but they can reveal which inputs the model relies on most. In the present thesis, permutation importance was particularly informative because it quantified the decline in model performance after random disruption of each feature. The finding that anticoagulant therapy ranked as the most important predictor strengthens the coherence between conventional regression and machine-learning outputs. Still, future work should include external validation, calibration analysis, and prospective implementation to determine whether such a model can improve real-world decision making [14,33,36].

1.5 Multimorbidity, frailty, and competing risks in the aging AF population

Atrial fibrillation in the oldest old should be interpreted through a geriatric rather than a purely electrophysiological lens. In this age stratum, frailty, sarcopenia, disability, sensory impairment, falls, and reduced physiological reserve shape both clinical presentation and prognosis. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing

age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [1-8]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, the combination of irregular rhythm, reduced cardiovascular reserve, systemic inflammation, and multimorbidity may lower the threshold at which the aging brain becomes vulnerable to ischemic and hypoperfusion-related injury. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Frailty also complicates follow-up, because gait slowing, undernutrition, low social support, and subclinical cognitive deficits may precede overt dementia and may already interfere with anticoagulation monitoring or medication persistence. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, in frail patients, the comparative advantages of simpler drug regimens, lower intracranial bleeding rates, and the absence of INR variability become

especially relevant when cognitive preservation is viewed as a treatment objective rather than an incidental benefit. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

Frailty variables often interact with age, comorbidity, nutrition, blood pressure, renal function, and inflammatory status, making a multidimensional approach preferable to single-risk labels. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Most elderly patients with AF do not experience the arrhythmia in isolation but within a dense network of competing chronic diseases, including hypertension, diabetes, coronary disease, chronic kidney disease, lung disease, and heart failure. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [1-4,11-13]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a

biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, shared vascular injury, neurohormonal activation, oxidative stress, and chronic low-grade inflammation create a background in which multiple organs age together and may amplify each other's dysfunction. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

A patient may remain free from major stroke yet still accumulate repeated insults through blood-pressure lability, renal impairment, subclinical embolism, and reduced cerebral reserve; this is exactly the type of longitudinal complexity that conventional disease labels often conceal. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, when anticoagulant treatment is embedded in multimorbidity, practical issues such as polypharmacy, drug interactions, clinic attendance, and monitoring burden may influence outcomes almost as much as nominal drug efficacy. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at

least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

Prediction of cognitive decline in such patients benefits from models capable of handling correlated predictors and mixed data types rather than assuming that one dominant variable explains the entire trajectory. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Hypertension remains one of the most prevalent comorbidities in AF and one of the most plausible amplifiers of subsequent brain injury. Its relevance extends far beyond stroke counting because long-term exposure to elevated and unstable blood pressure promotes arterial stiffness, endothelial dysfunction, and small-vessel remodeling. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [3-4,12-13]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, chronic pulsatile stress damages cerebral arterioles, impairs autoregulation, favors white-matter injury, and increases susceptibility both to lacunar ischemic lesions and to hemorrhagic microangiopathy. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

In clinical practice, blood-pressure burden is rarely static: older adults may alternate between sustained hypertension, orthostatic episodes, and overtreatment-related hypotension, each of which can influence cerebral perfusion and cognitive symptoms. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, for anticoagulated AF patients, the coexistence of hypertension may intensify the consequences of labile anticoagulation by increasing the background risk of both ischemic and hemorrhagic cerebral lesions. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The prominence of systolic blood pressure among the model's most informative predictors is therefore biologically coherent and supports the view that brain protection in AF requires tight attention to vascular load, not only to rhythm and anticoagulant class. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Diabetes mellitus and insulin resistance occupy a central position in the cardiometabolic profile of elderly AF patients. Their effects are cumulative and systemic, involving vascular injury, endothelial dysfunction, oxidative stress, low-grade inflammation, and altered cellular energetics. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [11-13,31]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, hyperglycemia and insulin resistance may accelerate blood-brain barrier dysfunction, microvascular disease, and neuronal susceptibility to ischemic stress, while also worsening the vascular substrate on which AF-related injury occurs. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on

cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Clinically, diabetes rarely acts alone. It often accompanies obesity, dyslipidemia, chronic kidney disease, and hypertension, thus creating a tightly interconnected risk cluster that may drive progressive cognitive deterioration even in the absence of a clinically recognized stroke. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, because dietary complexity, renal dose adjustment, and polypharmacy may affect treatment continuity, metabolic disease can also indirectly influence the comparative performance of anticoagulant strategies over long follow-up windows. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The emergence of glycemia among the most influential predictors in the Random Forest model strongly supports this integrated interpretation and suggests that metabolic control should be read as a determinant of brain aging in AF rather than as a background covariate only. Conventional regression remains essential for estimating adjusted associations, but it

may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Renal dysfunction is particularly relevant in elderly AF because it lies at the crossroads of thrombosis, bleeding, inflammation, endothelial injury, and therapeutic complexity. Chronic kidney disease is also a well-recognized marker of biological aging and of diffuse vascular disease. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [12,28-30]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, the renal-brain axis involves uremic toxicity, oxidative stress, arterial calcification, impaired endothelial repair, altered platelet function, and dysregulated microcirculation, all of which can contribute to silent cerebrovascular damage and cognitive decline. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction,

and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

In routine care, declining renal function may change drug exposure, adherence, dose selection, and the safety margin of anticoagulation. This creates a dynamic setting in which longitudinal treatment quality may differ meaningfully between VKAs and NOACs, particularly in older populations. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the possibility that some direct oral anticoagulants may be associated with a more favorable renal trajectory than VKAs is therefore not a peripheral issue; it is potentially linked to the broader question of whether treatment class influences long-term brain outcomes [29-30]. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

From a modeling perspective, renal variables may not show isolated dramatic effects yet still participate in important interaction patterns with age, blood pressure, albumin, potassium, and metabolic burden. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well

suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Heart failure and AF frequently coexist, and their combination may be particularly harmful for the brain. When atrial contraction is lost and ventricular rhythm becomes irregular, beat-to-beat variability in forward flow may impair cerebral perfusion, especially in patients with already reduced cardiac output or impaired vascular reserve. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [3-4,9-10,21,24]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, reduced atrial transport, neurohormonal activation, myocardial remodeling, and impaired vascular responsiveness create a hemodynamic context in which vulnerable cerebral regions may experience chronic relative hypoperfusion. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This mechanism is clinically attractive because it explains why some patients show cognitive decline even without overt embolic events. Memory circuits, temporal regions, and

subcortical networks may be affected by prolonged exposure to unstable flow and reduced reserve. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, therapeutic comparisons between VKAs and NOACs do not directly solve hemodynamic dysfunction, yet treatment simplicity and the avoidance of major bleeding may still influence downstream trajectories by reducing interruption, instability, and event burden. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This perspective interprets AF-related brain injury not as exclusively embolic but as partly hemodynamic, reinforcing the need for models that can integrate rhythm, comorbidity, laboratory, and treatment-related information in the same predictive space. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

1.6 Covert brain injury, endothelial dysfunction, and biological mediators

One of the most important conceptual changes in the field has been the recognition that clinically silent brain lesions are not clinically irrelevant. Silent cerebral infarction is common in AF and has repeatedly been linked to measurable cognitive consequences. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [16-20,23,40]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, small embolic or hypoperfusion-related lesions may interrupt white-matter tracts, subcortical-frontal circuits, and strategic cortical networks without producing an obvious focal neurological syndrome. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

The resulting phenotype is often gradual rather than dramatic: slowed processing speed, reduced executive efficiency, poorer attention, and vulnerability to later major neurocognitive disorder. This is particularly important in elderly patients, in whom baseline reserve may already be limited. In older adults, even a modest decline in global cognition

may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, any anticoagulant strategy capable of reducing cumulative covert ischemic injury could therefore be relevant to cognition even when annual stroke rates appear low. Conversely, unstable anticoagulation may permit continued silent lesion accrual that remains invisible unless longitudinal cognitive testing or neuroimaging is performed. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The emphasis placed here on serial MMSE assessment and on machine-learning prediction is closely aligned with this concept of hidden but accumulating network injury. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Cerebral microbleeds represent the hemorrhagic mirror of covert ischemic injury. In elderly anticoagulated patients, they signal underlying small-vessel fragility and may coexist with white-matter disease, lacunes, and diffuse endothelial dysfunction. In epidemiological terms,

this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [20,24-25,27-30]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, microangiopathic fragility, amyloid-related vascular change, hypertension-related arteriopathy, and episodes of over-anticoagulation may all contribute to a brain environment in which microscopic hemorrhagic damage accumulates over time. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

From a cognitive perspective, the importance of microbleeds lies not only in their association with future intracranial hemorrhage but also in the fact that they reflect diffuse vascular injury and may participate in network-level dysfunction. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this mechanism adds a second dimension to the NOAC-VKA comparison. The question is not only which therapy prevents embolism more effectively, but also which is less likely to expose the patient to a chronic burden of hemorrhagic microinjury under real-world conditions. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

A brain-centered interpretation therefore adopts a brain-centered rather than event-centered interpretation of anticoagulation quality, recognizing that covert hemorrhagic injury may be as relevant to long-term cognition as overt stroke. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Endothelial dysfunction provides a powerful unifying concept for understanding why AF, vascular disease, and cognitive decline so often coexist. The endothelium regulates vascular tone, thrombosis, inflammation, permeability, and tissue perfusion; when chronically injured, its dysfunction is expressed across several organs simultaneously. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia

control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [12,24,26,32,39]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, impaired nitric-oxide signaling, pro-adhesive activation, inflammatory cell recruitment, and a shift toward a prothrombotic phenotype may facilitate both atrial thrombogenesis and cerebral microvascular damage. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

In the brain, endothelial dysfunction may increase blood-brain barrier permeability, weaken autoregulation, and intensify the consequences of metabolic stress or intermittent hypoperfusion. It thereby serves as a plausible amplifier of both vascular cognitive impairment and neurodegenerative vulnerability. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, experimental studies suggesting direct endothelial effects of factor Xa inhibition are therefore of translational interest, because they hint that some benefits of NOACs may not be limited to anticoagulation kinetics alone [32,39]. Where

anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

For predictive modeling, endothelial dysfunction is rarely captured by a single laboratory value; instead, it is indirectly reflected through patterns involving albumin, renal function, blood pressure, inflammatory biomarkers, and clinical vascular disease. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

The acute ischemic stroke component of this work is rooted in the modern concept of immunothrombosis, according to which coagulation and inflammation are not separate processes but mutually reinforcing biological programs. This perspective is highly relevant in AF, where thrombogenesis develops within a systemic inflammatory and endothelial context. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [12,26,41]. Accordingly, this work interprets the AF population not as a

homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, platelet activation, thrombin generation, leukocyte recruitment, and endothelial injury interact rapidly after arterial occlusion and shape both the extent of tissue damage and the downstream biological signature detectable in blood. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This framework helps explain why a multimarker panel is preferable to a single molecule when attempting to phenotype stroke biologically. Different analytes reflect different portions of the same event: thrombotic activation, inflammatory remodeling, endothelial stress, neuronal injury, and glial response. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the substudy involving PF4, OPN, UCH-L1, IP-10, sCD141, GFAP, and FABP3 should therefore be understood not as a detached ancillary analysis but as an event-level window into the molecular processes that may also contribute to long-term cognitive deterioration. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may

plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

By linking acute biomarker biology to chronic cognitive trajectories, the work advances a translational model in which cerebrovascular events are interpreted as part of a continuum rather than isolated endpoints. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Blood biomarkers of neuroglial injury are attractive because they may provide information that conventional clinical examination cannot fully capture in the hyperacute or early subacute phases of stroke. They are particularly useful when the objective is not only diagnosis but also biological characterization. In epidemiological terms, this issue is highly relevant because AF prevalence, cumulative exposure to comorbidity, and vulnerability to disability all rise with advancing age and with the broad cardiovascular transition described in contemporary population studies. Guideline documents increasingly emphasize that AF management must move beyond arrhythmia control and include structured evaluation of long-term outcomes, comorbidity clustering, and patient-centered goals, including preservation of cognition and function [12,26,41]. Accordingly, this work interprets the AF population not as a homogeneous anticoagulated cohort, but as a biologically diverse group in whom different trajectories of cerebral aging may coexist from the outset.

Mechanistically, markers such as UCH-L1 and GFAP reflect different cellular compartments and temporal patterns of injury, while OPN and PF4 speak more directly to inflammatory and thrombotic activation. Rather than acting through a single pathway, these

factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

The relevance of this approach lies in its capacity to add biological depth to a clinically driven study. If event-related markers distinguish patients and correlate with disease mechanisms, they help explain why certain AF trajectories may culminate in stroke and accelerated cognitive decline. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, at the same time, biomarker studies demand caution: timing of sampling, pre-analytical handling, coexisting renal dysfunction, and stroke heterogeneity can all influence concentrations and their apparent diagnostic value. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

For this reason, the work treats biomarkers as mechanistic enhancers of interpretation rather than as standalone replacements for imaging or clinical judgment. Conventional regression

remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Neuroimaging has been central in shifting the discussion from overt stroke to covert brain injury. MRI studies in AF have documented silent infarcts, white-matter abnormalities, hippocampal atrophy, and broader structural correlates of reduced cognitive performance. These findings acquire particular relevance in aging populations, in whom rising AF prevalence and cumulative comorbidity magnify exposure to subclinical cerebral damage and later disability [18-20,23,40]. Contemporary management frameworks therefore extend beyond arrhythmia control alone and increasingly incorporate long-term outcomes, multimorbidity, and preservation of cognition and function. Within this perspective, AF is best regarded as a biologically heterogeneous condition in which different trajectories of cerebral aging may coexist from the outset.

Mechanistically, these lesions likely represent the combined effects of embolism, chronic perfusion instability, small-vessel disease, and pre-existing neurodegenerative vulnerability. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Clinically, the major challenge is that imaging is not performed serially in all patients, and many lesions remain undetected outside research settings. As a result, longitudinal cognitive testing often becomes the most practical proxy for cumulative brain injury in real-world cohorts. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this makes the interpretation of anticoagulant therapy more complex. A patient may show preserved independence and no clinical stroke history while nonetheless harboring a significant burden of covert lesions that differ according to treatment quality and vascular comorbidity. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This perspective therefore positions cognitive decline as an accessible clinical readout of otherwise hidden structural injury, while acknowledging that future studies should ideally integrate serial imaging with predictive modeling. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Cognitive decline is not a uniform process. Patients with similar vascular burden may show markedly different trajectories according to education, premorbid reserve, social engagement, sensory status, baseline brain pathology, and cumulative medical stress. This heterogeneity is clinically crucial in older adults with AF, because increasing age and multimorbidity amplify both cerebral vulnerability and the consequences of even modest cognitive deterioration [11,15-17,22]. Current clinical thinking therefore favors a broader and more individualized view of AF management, in which preservation of cognition and function is considered alongside classical vascular outcomes. The AF population should consequently be interpreted not as a homogeneous anticoagulated cohort, but as a biologically diverse group with distinct patterns of reserve, resilience, and decline.

Mechanistically, reserve-related differences may delay the clinical expression of structural injury, meaning that two patients with comparable lesion burden can perform differently on screening tools and may cross the threshold of impairment at different times. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This heterogeneity is highly relevant for AF research because it cautions against simplistic interpretations of both baseline MMSE and follow-up change. A stable score does not always mean absence of vulnerability, and a modest decline may be clinically meaningful in a patient whose daily autonomy depends on complex self-management. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration

should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, therapeutic implications follow naturally. If cognition is understood as a dynamic reserve-dependent outcome, then prevention of small recurrent insults becomes even more important, because preserving reserve may matter as much as preventing catastrophic events. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The machine-learning approach adopted here is particularly compatible with such heterogeneity, since it does not assume that all patients deteriorate along the same path or at the same speed. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Population studies have made it clear that AF is not epidemiologically uniform across sex, ethnicity, socioeconomic position, or healthcare system context. Lifetime risk estimates, age at presentation, access to screening, and treatment patterns all vary across populations. These differences matter for cognitive outcomes because the burden of vascular exposure, competing risk, and diagnostic opportunity is unevenly distributed across demographic and healthcare settings [1-8]. For this reason, contemporary AF research increasingly

emphasizes population heterogeneity, patient-centered outcomes, and the need to interpret cerebral aging within a broader clinical and social context rather than through arrhythmia status alone.

Mechanistically, these differences likely reflect a combination of biological predisposition, comorbidity profiles, healthcare access, social determinants, and competing risk structures rather than a single explanatory mechanism. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

In cognitive research, such heterogeneity matters because the apparent relationship between AF and decline may be modified by education, survival bias, baseline reserve, or under-recognition of covert brain injury. Older patients and socially vulnerable patients may be especially prone to underdiagnosis. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the real-world observational design is a strength because it reflects the clinical mixture encountered in tertiary and outpatient practice rather than an artificially simplified trial population. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant

profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

At the same time, this heterogeneity is another argument for cautious interpretation of observational findings and for the use of models capable of incorporating multiple interacting determinants rather than relying on a universal linear effect. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Adherence and persistence are often discussed as practical issues, yet in elderly AF they are integral biological determinants of long-term brain protection. The real efficacy of anticoagulation depends on sustained exposure to treatment, appropriate dosing, and the patient's ability to navigate long care pathways. In older and multimorbid populations, failures of adherence are not marginal events: they can reshape thromboembolic protection, bleeding risk, and ultimately the cumulative burden of covert cerebrovascular injury [3-4,27-30]. This makes treatment continuity part of the pathophysiological chain linking anticoagulant strategy to long-term cognitive outcomes rather than a merely administrative variable.

Mechanistically, cognitive vulnerability, sensory deficits, social isolation, medication complexity, transportation barriers, and fluctuating health status can all reduce persistence and create periods of inadequate protection. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may

remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

These problems are magnified in VKA-based care, where INR monitoring, dietary interactions, and frequent dose changes may place a greater burden on patients, caregivers, and health systems. Even when warfarin is theoretically effective, real-world instability may diminish that benefit. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, nOAC-based strategies may therefore confer advantages that are partly organizational: fewer monitoring demands, simpler routines, and potentially more continuous anticoagulant exposure. Such differences are highly relevant when the outcome of interest unfolds over years rather than days. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

Adherence is interpreted not merely as a compliance variable but as part of the mechanism through which treatment class may influence cognitive trajectories. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent

threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

If cognitive decline in AF is gradual, multifactorial, and often clinically silent in its early phase, then one-time cognitive screening is insufficient. Serial assessment becomes essential for distinguishing baseline vulnerability from true longitudinal deterioration. In this setting, repeated cognitive evaluation has value not only for prognosis but also for care organization, because evolving impairment may alter adherence, symptom reporting, and the feasibility of complex therapeutic regimens [3-4,15-17,22]. Longitudinal assessment therefore complements vascular risk stratification by capturing a clinically meaningful dimension of brain health that may otherwise remain underrecognized.

Mechanistically, repeated cognitive testing allows the clinician to capture small downward shifts, correlate them with intercurrent events or treatment changes, and identify patients whose autonomy may be beginning to erode before frank dementia develops. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

From a service perspective, incorporating cognition into AF follow-up also has practical value. Patients with emerging deficits may need simplified medication plans, stronger caregiver involvement, closer adherence support, or reassessment of the feasibility of complex therapeutic pathways. In older adults, even a modest decline in global cognition

may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the use of serial MMSE here should therefore be seen as a deliberate design choice aimed at maximizing longitudinal interpretability in a large real-world cohort, even while acknowledging the instrument's limitations. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This approach is aligned with current guideline thinking, which increasingly recognizes that long-term AF management must include patient-centered outcomes extending beyond stroke counts and hospitalization alone. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

The MMSE is often criticized because it is less sensitive than broader neuropsychological batteries for executive dysfunction, processing speed changes, or subtle domain-specific impairment. These limitations are real and should be acknowledged explicitly whenever cognition is assessed in large clinical cohorts. At the same time, the MMSE remains

practical, reproducible, and clinically interpretable in longitudinal settings, particularly when repeated measures are used to detect change over time rather than to define cognitive status at a single visit [15,22]. Within AF research, its value lies in providing a feasible window onto evolving brain vulnerability in populations for whom more extensive testing is often impractical.

Mechanistically, at the same time, the MMSE remains one of the most practical and standardized tools for repeated assessment in large multicenter cohorts, particularly when follow-up must remain feasible in older adults with variable mobility and education. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Its greatest strength in this context is not perfect diagnostic precision but reproducible longitudinal use. When applied within a consistent framework, changes over time can still provide clinically interpretable information about global cognitive trajectory. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this balance between practicality and imperfection mirrors the overall philosophy of the work: the goal is not to construct an idealized neuropsychological experiment but to study cognition in a real-world AF population followed over years. Where

anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

Accordingly, the results should be interpreted as evidence regarding longitudinal decline in a pragmatic clinical sense rather than as a definitive statement about the entire spectrum of neurocognitive domains. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

The question of whether NOACs preserve cognition better than VKAs is clinically important but methodologically difficult to answer through randomized evidence alone. Cognitive decline develops slowly, is influenced by many competing events, and may require years of follow-up and repeated testing to detect reliably. These features make cognition a demanding endpoint for conventional trial design and help explain why observational cohorts continue to provide important complementary evidence [3-4,27-30,33]. The issue is especially relevant in aging AF populations, where the cumulative effects of treatment quality, multimorbidity, and covert cerebrovascular injury may be more informative than any single acute event.

Mechanistically, mortality, treatment crossover, changes in adherence, silent lesions, and variable baseline reserve all complicate causal interpretation and can dilute true treatment

differences. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Even large randomized trials designed primarily for stroke prevention may be underpowered for cognitive endpoints or may not include the serial assessments needed to identify subtle decline. As a result, observational cohorts remain indispensable despite their inherent vulnerability to confounding. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this context justifies the dual methodological strategy adopted in the work: conventional adjusted analysis to estimate association and machine learning to explore multidimensional predictive structure. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

It also explains why results should be interpreted as building a strong clinical argument for brain-conscious anticoagulation rather than claiming to close the causal question once and

for all. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Machine learning in medicine is valuable only if it solves a clinically meaningful problem and does so transparently enough to be trusted. In AF-related cognitive decline, the problem is genuine: multiple weak and interacting predictors make prediction difficult with simple tools. Rather than replacing clinical judgment, computational models may help uncover nonlinear relations, threshold effects, and interactions among vascular, renal, metabolic, hemodynamic, and laboratory variables that are difficult to capture with conventional approaches alone [14,33-38]. This makes machine learning particularly attractive for studying heterogeneous geriatric cohorts in which neurocognitive risk emerges from cumulative rather than isolated determinants.

Mechanistically, ensemble methods such as Random Forest can capture nonlinearities, threshold effects, and higher-order interactions without requiring the investigator to specify all of them in advance. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

However, predictive performance alone is insufficient. Clinicians must understand why a model behaves as it does, whether its operating threshold is appropriate, and whether it

identifies a clinically interpretable risk phenotype rather than a statistical artifact. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this is why feature importance, cross-validation, class-imbalance strategies, and transparent reporting standards occupy a central place in the methodological architecture of the work. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The aim is not to replace clinical reasoning with automation, but to use computational tools to reveal patterns that may otherwise remain obscured within complex geriatric datasets. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

In imbalanced clinical datasets, a model may appear accurate while still failing the patients who matter most. This is particularly true when the positive class consists of individuals who will develop cognitive decline and who may benefit from closer surveillance. For this reason,

predictive performance in AF-related cognition should be judged with attention to sensitivity, calibration, class balance, and clinical usefulness rather than with global accuracy alone [14,33,36-38]. Methodological rigor is essential if predictive tools are to inform a genuinely brain-conscious approach to risk stratification.

Mechanistically, the default classification threshold often privileges specificity and may produce an apparently reassuring model that misses a substantial number of vulnerable patients. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Threshold optimization is therefore not merely a statistical adjustment; it is a clinically and ethically relevant decision about the balance between false reassurance and over-alerting. In many longitudinal care settings, greater sensitivity may be preferable if the downstream action is non-invasive monitoring or preventive intensification. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the performance analyses here, including class weighting, SMOTE, precision-recall metrics, and threshold adjustment, reflect exactly this logic. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient

thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

They show that predictive modeling for cognition should be calibrated to clinical purpose rather than judged solely by a single summary statistic such as overall accuracy. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

A major strength of this approach is that it extends toward a translational interpretation of risk. Clinical prediction and biomarker phenotyping are presented as complementary rather than competing approaches. This integration is especially relevant in AF, where endothelial dysfunction, inflammation, covert brain injury, and treatment-related factors may converge within the same patient but with different relative weights over time [12,14,26,33,36,41]. A multidimensional framework therefore offers a more plausible representation of neurocognitive risk than models that isolate single mechanisms or single categories of variables.

Mechanistically, clinical variables describe the patient's chronic vulnerability, whereas event-related biomarkers reveal the biological intensity and character of acute injury when stroke occurs. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the

association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This combination is conceptually powerful because it allows the clinician to think across time scales. One set of data explains who is vulnerable over years; another helps explain what happens biologically when vulnerability culminates in a cerebrovascular event. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, future models may therefore be able to integrate demographics, treatment class, renal and metabolic markers, imaging, and acute biomarker panels into a more refined precision framework. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This approach provides an important step in that direction by demonstrating that both long-term predictive structure and mechanistic biomarker signal can be identified within the same research program. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why

particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

1.7 Atrial cardiomyopathy, aging, and multidimensional phenotyping

The concept of atrial cardiomyopathy has become increasingly useful because it repositions AF as a manifestation of broader atrial disease rather than a rhythm disturbance alone. Structural remodeling, fibrosis, stretch, altered conduction, and impaired contractility all contribute to thrombogenesis and arrhythmia maintenance. This model is particularly relevant for cognitive outcomes because it links arrhythmia burden to a wider substrate of endothelial dysfunction, embolic propensity, and systemic remodeling rather than to rhythm alone [3-4,9-10,21]. AF-related cerebral vulnerability can therefore be interpreted as part of a broader cardiovascular phenotype with heterogeneous biological expression.

Mechanistically, this diseased atrial substrate reflects wider systemic injury driven by hypertension, obesity, diabetes, heart failure, and inflammatory signaling. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Seen from this perspective, the atrium becomes both a source of embolism and a marker of generalized cardiovascular remodeling. The same processes that damage the atrium may also damage the cerebral microcirculation and reduce tolerance to hemodynamic stress. In older adults, even a modest decline in global cognition may translate into poorer treatment

adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, this model strengthens the rationale for studying cognition in AF longitudinally, because it suggests that arrhythmia, stroke, and cognitive decline are different expressions of a shared disease network. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

It also supports the use of multidimensional prediction, since treatment class is only one element operating within a much broader pathological substrate. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

The Mediterranean clinical context in which many elderly AF patients are managed is characterized by rapid demographic aging, high prevalence of vascular risk factors, and substantial heterogeneity in social and family support. These contextual elements influence both disease presentation and follow-up feasibility. In this setting, cognitive trajectories are shaped not only by arrhythmia and comorbidity but also by continuity of care, caregiver

availability, nutritional patterns, and health-system organization [1-4,11-12]. The regional context therefore adds explanatory depth to any interpretation of long-term cognitive outcomes in AF.

Mechanistically, dietary habits, comorbidity clustering, socioeconomic conditions, and healthcare access can shape the balance between resilience and vulnerability even when headline diagnoses appear similar. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

For cognition research, this matters because the effects of AF, stroke burden, and anticoagulation may unfold differently according to reserve, social support, and control of concomitant vascular disease. A purely disease-centered model may therefore miss important real-world determinants of decline. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, a comprehensive assessment grounded in this geriatric reality is essential, because management decisions occur within families, outpatient systems, and long-term care pathways. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant

profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This perspective further justifies the choice of pragmatic longitudinal assessment and the emphasis on prediction tools that can function within routine clinical complexity. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Polypharmacy is almost unavoidable in older patients with AF, yet its cognitive implications are often underestimated. Multiple cardiovascular and non-cardiovascular drugs can affect blood pressure stability, renal function, adherence, and the patient's capacity to manage treatment safely. In multimorbid older adults, prescribing complexity may interact with frailty, sensory impairment, and caregiver dependence, thereby influencing both treatment quality and exposure to cerebral risk [3-4,28-30]. Polypharmacy should therefore be considered part of the multidimensional architecture through which AF management may shape cognitive trajectories.

Mechanistically, drug-drug interactions, inappropriate prescribing, treatment fatigue, and fluctuating dosing complexity may convert otherwise effective therapies into unstable real-world exposure patterns. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt

stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This is particularly relevant when comparing VKAs and NOACs, because the organizational simplicity of the latter may reduce part of the therapeutic friction associated with long-term anticoagulation in older adults. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, polypharmacy also interacts with baseline cognition: the more cognitively vulnerable the patient, the higher the risk that medication complexity itself becomes a determinant of outcome. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

By situating treatment class within the broader ecology of prescribing quality, the work strengthens its interpretation of anticoagulant choice as part of a multidimensional care strategy rather than a single pharmacological decision. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning

approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Routine cognitive assessment in AF raises ethical as well as clinical questions. Detecting early decline has value only if it leads to practical adaptations in care, communication, support, and treatment planning. In older adults receiving anticoagulation, cognitive information may influence how instructions are delivered, whether caregivers are involved, and how follow-up is structured, thereby affecting both safety and therapeutic continuity [3-4,15,22]. The goal is not to use cognition as an exclusion criterion, but to incorporate it into a more individualized and feasible model of care.

Mechanistically, screening without follow-through risks labeling vulnerability without improving outcomes, whereas thoughtful integration of cognitive information can help align therapy with the patient's real capacity for self-management. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

In anticoagulated older adults, this may influence how medication instructions are delivered, whether caregivers are engaged, how often follow-up is scheduled, and how clinicians judge the feasibility of complex monitoring pathways. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

From this perspective, cognition should be assessed not to exclude patients from treatment but to optimize treatment around their needs and risks. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

This organizational dimension is crucial because preserving brain health in AF depends as much on sustained, comprehensible care as on the pharmacology of any single drug. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Classical AF care has been shaped by risk scores such as CHA2DS2-VASc and HAS-BLED, which remain clinically indispensable. However, these tools were not designed to represent the full complexity of long-term neurocognitive risk. Prediction of cognitive decline requires attention to multimorbidity, treatment quality, reserve, frailty, biological injury, and nonlinear interactions across domains that are only partially represented in conventional scores [3-4,14,33-38]. This limitation provides a strong rationale for multidimensional models capable of integrating variables from different levels of the heart–brain axis.

Mechanistically, stroke scores summarize important vascular determinants, but they do not directly capture covert brain injury, treatment persistence, subtle metabolic patterns, or nonlinear combinations of vulnerability factors. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may

remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

This limitation does not diminish their value; rather, it defines the space in which additional predictive approaches may contribute. A multidimensional phenotype can coexist with classical scores and may be especially helpful when the outcome of interest is cognition rather than a single acute event. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, machine learning is therefore treated as an extension of clinical stratification rather than a replacement for established bedside tools. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

Its contribution lies in showing that treatment class, laboratory data, and cardiometabolic features together can define a more nuanced risk architecture than conventional scores alone. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic,

renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

1.8 Integrative synthesis toward brain-conscious AF management

Taken together, the literature reviewed in this introductory chapter supports a unifying idea: AF should be managed with explicit attention to the brain as a long-term target organ. Stroke prevention remains fundamental, but it is only one part of a broader objective that includes preservation of cognition, autonomy, and biological reserve. A brain-conscious perspective on AF integrates multimorbidity, covert cerebrovascular injury, inflammation, treatment quality, and longitudinal functional outcomes within the same clinical framework [3-4,12,14,16-20,23-30,33-38,41]. Such an approach also provides a more coherent basis for evaluating whether different anticoagulant strategies may influence cognitive trajectories over time.

Mechanistically, embolic injury, silent infarction, microbleeding, hypoperfusion, endothelial dysfunction, inflammation, renal impairment, metabolic disease, and treatment complexity all contribute to the final cognitive phenotype. Rather than acting through a single pathway, these factors tend to interact over time, creating cumulative brain vulnerability that may remain clinically silent for years before becoming evident on cognitive testing. This is one of the key reasons why the association between AF and cognitive decline persists even after adjustment for overt stroke in several observational studies, and why silent lesions, perfusion instability, endothelial dysfunction, and systemic inflammation have become central explanatory concepts in the field [12,16-20,23-26].

Within this framework, the NOAC-VKA comparison becomes clinically meaningful not simply because it concerns anticoagulation efficacy, but because it may shape the cumulative exposure of the brain to preventable injury over years of follow-up. In older adults, even a modest decline in global cognition may translate into poorer treatment adherence, reduced capacity to report symptoms accurately, lower tolerance of complex therapeutic regimens, and progressive dependence in daily activities. For that reason, cognitive deterioration should not be considered a secondary or merely descriptive endpoint in AF; it should be regarded as a clinically relevant expression of cumulative vascular and systemic injury [3-4,15,22,24].

Regarding anticoagulation, the machine-learning component of the work is justified precisely by this complexity: it seeks to integrate multiple modest predictors into a clinically useful estimate of risk while retaining interpretability. Where anticoagulation quality is unstable, the brain may be exposed not only to insufficient thromboembolic protection but also to episodic over-anticoagulation and hemorrhagic microinjury. By contrast, a more predictable anticoagulant profile may plausibly reduce at least part of the long-term burden of covert ischemic and hemorrhagic brain damage, although observational studies require cautious interpretation and cannot by themselves establish causality [27-30,32,39].

The chapters that follow move from this conceptual background to the concrete aims, methods, results, and implications of the multicenter study and its biomarker substudy. Conventional regression remains essential for estimating adjusted associations, but it may not fully represent threshold effects, nonlinear relations, or interactions among metabolic, renal, hemodynamic, and laboratory variables. This is why particular emphasis is placed on supervised machine-learning approaches, which are well suited to multidimensional geriatric data and can complement classical inferential models when evaluated with transparent reporting standards [14,33-38].

Aging is accompanied by a chronic low-grade inflammatory state often described as inflammaging. In elderly AF patients, this background may intensify the thrombo-inflammatory profile already promoted by arrhythmia, metabolic disease, and endothelial dysfunction. In parallel, nutritional status and electrolyte balance may modulate frailty, vascular stability, arrhythmic burden, and susceptibility to cerebral injury, thereby contributing to interindividual variability in cognitive outcomes [11-12,26,31]. These dimensions broaden the heart–brain framework by linking systemic aging biology to the clinical expression of neurocognitive decline.

Mechanistically, age-related immune activation, cytokine imbalance, oxidative stress, and impaired resolution of inflammation may enhance vascular injury, reduce endothelial resilience, and sensitize neural tissue to ischemic and hypoperfusion-related damage. These pathways may remain partially latent for years, producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, this perspective reinforces the view that cognitive decline in AF is not solely a vascular plumbing problem, but also an immunobiological process unfolding over years. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, therapies that reduce treatment instability and perhaps attenuate endothelial activation may indirectly interact with this inflammatory background, although such effects require cautious interpretation and further translational confirmation. This line of reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

Incorporating markers and proxies of systemic vulnerability is methodologically attractive because inflammatory aging is rarely captured by one variable alone and is more likely to

emerge through patterns of laboratory and clinical interaction. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

Nutritional status is often overlooked in cardiovascular cohorts, yet it can influence cognition, frailty, inflammation, drug handling, and recovery capacity. Serum albumin, in particular, may reflect a composite of nutrition, inflammation, liver function, systemic illness, and biological reserve. This theme is especially relevant in older AF populations, where long exposure to vascular and systemic stress may reshape brain vulnerability long before a formal neurological diagnosis is made. Contemporary literature increasingly supports the idea that cognition in AF reflects the cumulative effect of several converging processes rather than the mere occurrence of a single major embolic event [11-12].

Mechanistically, malnutrition, chronic inflammation, and catabolic stress can reduce vascular and neural resilience, thereby increasing the impact of otherwise modest ischemic or hemodynamic insults. These pathways may remain partially latent for years, producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, in elderly AF patients, low resilience may manifest as poorer recovery after intercurrent illness, greater treatment complexity, and lower tolerance of physiological stressors that would be compensated more easily in fitter individuals. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, the prominence of albumin among influential predictors in the Random Forest model is therefore clinically plausible and supports reading this biomarker as part of a broader resilience phenotype rather than a laboratory detail. This line of

reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

Nutritional and inflammatory proxies may help machine-learning models identify patients whose long-term cognitive risk is amplified by systemic vulnerability that standard cardiovascular scores do not directly capture. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

Electrolyte balance is another underappreciated component of vulnerability in AF. Potassium, in particular, sits at the intersection of renal function, diuretic exposure, neurohormonal activation, arrhythmic stability, and overall physiological reserve. This theme is especially relevant in older AF populations, where long exposure to vascular and systemic stress may reshape brain vulnerability long before a formal neurological diagnosis is made. Contemporary literature increasingly supports the idea that cognition in AF reflects the cumulative effect of several converging processes rather than the mere occurrence of a single major embolic event [3-4,28-30].

Mechanistically, disturbances in electrolyte homeostasis may signal broader instability involving renal dysfunction, heart failure, medication burden, and acute-on-chronic stress, all of which can influence cerebral perfusion and treatment safety. These pathways may remain partially latent for years, producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, while potassium itself is not a direct biomarker of cognitive decline, its predictive importance may indicate that subtle physiologic disequilibrium is part of the phenotype of patients who deteriorate cognitively over time. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, this observation is especially relevant in older anticoagulated patients, in whom recurrent minor derangements may cluster with other vulnerabilities and may reflect the same fragility that complicates long-term management. This line of reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

Machine-learning approaches are particularly useful for such variables because they can reveal predictive value even when the biological meaning resides in interaction patterns rather than in a single linear causal pathway. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

A further layer of complexity arises from the fact that cognitive impairment may already be present before an overt AF-related ischemic event occurs. In many patients, the brain is already vulnerable when stroke finally becomes clinically manifest. This pre-stroke vulnerability reinforces the view that cognition in AF reflects cumulative injury developing over time rather than the isolated consequence of a single embolic episode [12,15,22,40]. It also supports interest in digital health and remote longitudinal phenotyping, which may facilitate earlier recognition of decline, treatment difficulties, and evolving functional dependence outside traditional hospital-based follow-up.

Mechanistically, pre-existing network injury, reduced reserve, silent lesions, and subclinical neurodegenerative change may shape both acute presentation and post-stroke recovery, making outcome a function of baseline vulnerability as much as event severity. These pathways may remain partially latent for years, producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, this means that stroke should not be viewed as the beginning of the cognitive story, but often as an acceleration within an ongoing trajectory of decline. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, the biomarker substudy therefore gains additional significance: by characterizing acute event biology in a population already exposed to chronic risk, it helps connect pre-event vulnerability with post-event consequences. This line of reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

Predictive frameworks that ignore baseline cognition are likely to underestimate true heterogeneity, whereas longitudinal designs such as the one used here are better positioned to capture how chronic and acute factors interact. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

Modern AF care is increasingly influenced by digital health, remote monitoring, and hybrid outpatient pathways. These developments are particularly important for elderly cohorts, in whom repeated in-person assessment may be limited by mobility, frailty, or caregiver dependence. This theme is especially relevant in older AF populations, where long exposure to vascular and systemic stress may reshape brain vulnerability long before a formal neurological diagnosis is made. Contemporary literature increasingly supports the idea that cognition in AF reflects the cumulative effect of several converging processes rather than the mere occurrence of a single major embolic event [2-4,14,36].

Mechanistically, remote follow-up, digital records, and structured longitudinal data collection can enrich phenotyping, support adherence surveillance, and reduce attrition in long-duration observational studies. These pathways may remain partially latent for years,

producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, the doctoral project itself incorporated remote follow-up options, reflecting an organizational awareness that high-quality geriatric research requires flexible methods of retaining contact with vulnerable patients over time. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, such infrastructure is also relevant to prediction modeling, because the usefulness of an algorithm depends on whether its input variables and outcome assessments can be collected reliably in real-world practice. This line of reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

The future clinical application of brain-conscious AF models will likely depend not only on statistical performance but also on the feasibility of integrating cognitive surveillance into routine and partially digital care pathways. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

1.9 Working hypothesis

This introductory framework leads to a precise working hypothesis. Elderly patients with non-valvular AF differ substantially in their predisposition to cognitive decline because they differ not only in age and stroke history, but also in the cumulative interaction of vascular burden, renal and metabolic dysfunction, frailty, treatment quality, and biological response to cerebrovascular injury. In this view, cognition in AF reflects the integrated effect of several converging processes rather than the mere occurrence of a single major embolic

event [3-4,12,14,16-20,23-30,33-38,41]. Consequently, models capable of combining clinical and molecular information may be better suited to identify patients at highest risk and to clarify whether different anticoagulant strategies are associated with distinct cognitive trajectories.

Mechanistically, the consequence is that cognitive decline should be predictable not from one canonical determinant, but from a multidimensional clinical-molecular pattern. These pathways may remain partially latent for years, producing silent or subclinical damage that only becomes visible when repeated testing, imaging, or biological phenotyping is performed.

From a clinical standpoint, within this pattern, anticoagulant class is expected to play a major role because it can modify the brain's cumulative exposure to covert ischemic and hemorrhagic injury across years of follow-up. For patients and caregivers, this means that apparently small changes in memory, executive function, or adherence capacity can have outsized consequences on treatment safety and long-term autonomy.

Regarding anticoagulation, the biomarker substudy complements this idea by suggesting that when stroke occurs, the event is biologically characterized by a recognizable thrombo-inflammatory and neuroglial signature rather than by a generic vascular insult. This line of reasoning helps explain why long-term cognitive differences between treatment strategies may emerge even when short-term event counts appear similar.

The following chapters therefore test a coherent translational model: NOAC-VKA choice, clinical vulnerability, and machine-learning integration may together define a more precise and clinically relevant approach to brain outcomes in AF. The rationale for combining conventional regression, machine-learning approaches, and mechanistic biomarker interpretation is precisely to capture this layered and longitudinal architecture of risk.

2. Aim of the study

2.1 Primary and secondary objectives

The doctoral project was designed to address a clinically relevant and insufficiently explored question: whether the type of oral anticoagulation in elderly patients with non-valvular AF influences the risk of longitudinal cognitive decline, and whether this risk can be predicted more effectively by integrating conventional clinical data with machine-learning methods. The primary objective was therefore to compare the evolution of cognitive function over time in patients treated with NOACs versus VKAs. The study was based on the hypothesis that NOAC therapy, owing to its greater pharmacological stability and lower burden of intracranial hemorrhagic complications, might be associated with slower deterioration in global cognitive performance.

A second objective was methodological: to develop a supervised machine-learning model capable of stratifying cognitive decline risk using demographic, clinical, hemodynamic, metabolic, and laboratory information. This objective stemmed from the recognition that cognitive deterioration in AF is unlikely to depend on a single dominant factor. Instead, it probably reflects a network of medium-effect predictors whose combined behavior is difficult to capture using linear approaches alone.

A third objective was translational and mechanistic. In patients experiencing ischemic stroke during follow-up, a biomarker substudy sought to explore whether acute thrombo-inflammatory, endothelial, and neuroglial markers could help characterize event-level biological signatures and support the pathophysiological plausibility of the broader clinical model. In this sense, the thesis deliberately joins longitudinal clinical epidemiology with molecular profiling. The machine-learning cohort provides the predictive core, whereas the stroke biomarker arm offers biological depth and a mechanistic bridge between arrhythmia, cerebrovascular injury, and subsequent cognitive vulnerability.

3. Materials and methods

3.1 Study design and setting

The clinical component of this thesis is based on a multicenter observational study enrolling consecutive elderly outpatients with non-valvular AF between January 2008 and September 2022. Participating centers included the University of Palermo (ProMISE Department / Internal Medicine and Stroke Care setting) and the University Magna Graecia of Catanzaro. The design was conceived to reflect routine clinical practice while preserving a structured framework for longitudinal reassessment. Because the target population was geriatric and clinically heterogeneous, the observational approach was appropriate for capturing the complexity of real-world treatment patterns and comorbidity profiles.

The doctoral project originally specified three principal clinical time points: baseline enrolment (T0), 36-month follow-up (T1), and 60-month follow-up (T2), with an additional event-driven assessment in the case of ischemic stroke during follow-up (T-stroke). This structure allowed the study to connect long-term cognitive trajectories with acute cerebrovascular phenotyping. In the final AF cohort analysis, follow-up was operationalized around baseline and subsequent cognitive reassessment, with decline defined as any reduction between baseline and the second MMSE evaluation. This harmonized the clinical design with the requirements of predictive modeling.

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the competent local committees, and written informed consent was collected from participants. The use of elderly patients required particular attention to consent procedures and to the feasibility of repeated follow-up assessments, including outpatient evaluation and, when necessary, remote contact for patients with reduced mobility.

3.2 Eligibility criteria and cohort assembly

Inclusion criteria were intentionally focused on elderly individuals with newly diagnosed non-valvular AF. Patients were eligible if they were 65 years of age or older, had a new diagnosis of AF, provided informed consent, and had sufficient follow-up for longitudinal analysis. Key exclusion criteria included valvular disease, prior oral anticoagulant therapy before enrolment, severe dementia or Alzheimer disease, psychiatric disorders or medications significantly affecting cognition, chronic infectious diseases, autoimmune systemic disorders, active cancer, and major hepatic failure. These criteria were chosen to reduce confounding from pre-existing advanced neurocognitive disease and from systemic conditions likely to profoundly alter inflammatory or survival profiles.

Across the study period, 1,366 patients were screened, and 983 were ultimately included in the AF cohort. Exclusions reflected age below threshold, prior anticoagulant exposure, mechanical prosthetic valves, significant mitral stenosis, cancer, cirrhosis, and chronic inflammatory disease. The resulting population represented a clinically meaningful elderly AF cohort with a broad burden of vascular and metabolic comorbidity but without obvious non-AF causes of severe cognitive deterioration at baseline.

3.3 Clinical variables and cognitive assessment

At baseline and during follow-up, participants underwent structured clinical evaluation including medical history, physical examination, electrocardiography, anthropometry, blood pressure measurement, and review of concurrent medications. The recorded covariates covered demographics, AF type, cardiovascular history, respiratory comorbidity, renal disease, metabolic status, hemodynamic variables, and established risk scores such as CHA2DS2-VASc and HAS-BLED. Laboratory variables included albumin, lipid profile, hemoglobin, platelets, sodium, potassium, creatinine, estimated glomerular filtration rate, NT-proBNP, fasting glucose, insulin, HOMA index, uric acid, and liver enzymes. The

intention was to capture a multidimensional clinical phenotype rather than a narrowly selected explanatory model.

Cognition was assessed with the MMSE. At baseline, patients were categorized as having normal cognition, borderline cognition, or mild cognitive impairment according to the study framework. Longitudinal cognitive decline was defined as any reduction in MMSE score between baseline and the second follow-up evaluation. This binary definition was selected because it is clinically intuitive and suitable for supervised classification. It also avoids dependence on arbitrary large cutoffs that might miss early decline.

For patients who developed ischemic stroke during follow-up, the doctoral protocol provided additional evaluation including NIHSS, modified Rankin Scale, Barthel Index, neuroimaging characterization, ASPECTS when appropriate, and etiologic classification by TOAST. This event-level assessment formed the bridge toward the molecular biomarker substudy.

3.4 Biomarker substudy

The molecular arm of the thesis focused on a panel of biomarkers selected to reflect complementary domains of acute ischemic brain injury. Osteopontin (OPN) was considered a marker of inflammatory matrix remodeling and leukocyte recruitment; platelet factor 4 (PF4) as an index of platelet activation and thrombo-inflammatory signaling; soluble thrombomodulin (sCD141) as a marker of endothelial injury; IP-10 as an inflammatory chemokine; UCH-L1 as a marker of neuronal injury; GFAP as a glial injury marker; and FABP3 as a marker potentially linked to tissue injury and metabolic stress. Blood samples were processed using ELISA-based quantification according to the original project framework.

Importantly, this biomarker analysis was not intended to replace the longitudinal AF cohort study. Rather, it complemented it by characterizing the subset of patients in whom a

cerebrovascular event occurred, thereby illuminating the biological processes that may connect AF-related vascular injury with downstream cognitive consequences. In the architecture of the thesis, the stroke biomarker arm therefore serves as a mechanistic extension of the main machine-learning study.

3.5 Statistical analysis and machine-learning pipeline

Two complementary analytical strategies were employed. First, multivariable logistic regression was used to assess whether anticoagulant class independently predicted cognitive decline after adjustment for potential confounders. This addressed the central comparative question using a clinically interpretable conventional model. Second, a supervised machine-learning approach based on Random Forest was implemented to capture more complex relationships across the predictor space.

Data preprocessing included standard clinical data curation, feature preparation, and treatment of class imbalance. Repeated stratified k-fold cross-validation was used to estimate model stability and generalization performance. Two strategies were explored for the imbalance problem: class weighting and SMOTE-based minority oversampling. Model performance was evaluated with ROC AUC, precision, recall, F1-score, and PR AUC. Because the intended use of the model concerned risk identification rather than mere global accuracy, threshold optimization was also performed. A threshold lower than the default 0.5 was examined to improve sensitivity for the decline class. Confusion matrices were generated to visualize misclassification patterns. Finally, permutation importance was applied to quantify the relative influence of each predictor on model performance.

The methodological choice of Random Forest was coherent with the clinical nature of the dataset. The cohort contained mixed categorical and continuous variables, multiple correlations, plausible nonlinear effects, and the possibility that treatment class might

interact with baseline vulnerability. Random Forest offered a robust balance between discrimination, flexibility, and interpretability for this type of structured clinical dataset.

4. Results

4.1 Baseline characteristics of the AF cohort

(tables 1-3)

The AF cohort comprised 983 elderly patients. Mean age was 76 ± 6 years, 49% were male, 8% were current smokers, 86% had hypertension, and 35% had type 2 diabetes mellitus. Overall, 692 patients (70%) were treated with NOACs and 291 (30%) with VKAs. Among NOAC recipients, dabigatran accounted for 27%, rivaroxaban for 38%, apixaban for 24%, and edoxaban for 11%. Baseline MMSE categories showed normal cognition in 58%, borderline cognition in 18%, and mild cognitive impairment in 24%, with no significant baseline difference in MMSE categories between treatment groups.

Despite comparable CHA2DS2-VASc scores, some baseline differences between treatment groups emerged. Patients receiving NOACs were younger, more frequently male, and had slightly lower body mass index than those receiving VKAs. Hypertension and respiratory failure/COPD were more common in the NOAC group, whereas diabetes, prior stroke/TIA, and ASCVD were more prevalent among VKA-treated individuals. HAS-BLED profiles also differed, indicating clinically relevant differences in bleeding risk distribution. As expected in a real-world observational cohort, concomitant medication patterns and several biochemical parameters also varied across treatment groups. These baseline differences justified the combined use of multivariable adjustment and machine-learning modeling.

Table 1: Baseline demographic and clinical characteristics.

Parameter	Whole population (n = 983)	VKAs (n = 291)	NOACs (n = 692)	p-Value
Demographic and clinical parameters				
Age, y	76 ± 6	77 ± 6	74 ± 5	<0.001
Sex (males), %	49	37	54	<0.001
BMI, kg/m²	29 ± 4	30 ± 3	29 ± 5	0.002
Smokers, %	8	9	7	0.27
Systolic BP, mmHg	133 ± 13	132 ± 10	133 ± 13	0.76
Diastolic BP, mmHg	77 ± 10	77 ± 9	77 ± 10	0.89
Pulse pressure, mmHg	56 ± 12	56 ± 11	56 ± 13	0.68
Atrial function, %				0.36
Paroxysmal	23	25	22	
Persistent	13	14	12	
Permanent	64	61	66	
PM or ICD, %	9	10	8	0.25
CHA2DS2-VASc (score)	4 (3–5)	4 (3–5)	4 (3–5)	0.48
MMSE (score), %				0.11
Normal (>25)	58	62	57	
Borderline (25)	18	14	19	
Moderate CI (<25)	24	24	24	
HAS-BLED, %				0.004
Low risk of bleeding	67	74	64	
High risk of bleeding	33	26	36	
Comorbidities				
Arterial hypertension, %	86	82	88	0.02
T2DM, %	35	41	33	0.01
Dyslipidemia, %	37	38	37	0.67
Respiratory failure/COPD, %	35	29	38	0.01
Heart failure, %	33	30	35	0.14
CKD, %	59	58	60	0.57
Sleep apnoea syndrome, %	26	24	27	0.25
Type of SAS, % (n = 257)				0.35
Obstructive (OSA)	42	48	40	
Central (CSA)	49	46	49	
Mixed (MSA)	9	6	11	
Severity of SAS, % (n = 257)				0.09
Mild	96	94	96	
Moderate	3	6	2	
Severe	1	0	2	
Liver disease, %	18	22	17	0.06
Previous stroke or TIA, %	13	9	14	0.02

Previous ACS, %	25	22	26	0.18
ASCVD, %	43	63	35	<0.001

Table 2: Baseline characteristics of patients (Medications).

Concomitant Medications	Whole population (n = 983)	VKAs (n = 291)	NOACs (n = 692)	p-Value
PPIs, %	79	86	76	0.001
Nitrates, %	6	4	7	0.09
ACEi/ARBs, %	77	81	75	0.03
β-blockers, %	60	67	57	0.005
Digitalis, %	15	13	16	0.18
Ca-channel blockers, %	15	15	15	0.94
MRAs, %	23	23	24	0.73
ARNI, %	26	25	26	0.74
Anti-arrhythmics drugs, %	17	20	15	0.04
Type of AAD drugs, %				0.05
None	83	80	85	
Amiodarone	6	5	6	
Flecainide	6	8	4	
Propafenone	4	5	4	
Other AAD drugs	1	2	1	
Metformin/OADs, %	23	21	23	0.47
Insulin, %	11	10	12	0.43
SGLT2i, %	22	25	20	0.12
GLP1-RAs, %	32	40	29	0.001
Lipid-lowering drugs, %	46	52	43	0.02
Previous antiplatelet, %	40	65	30	<0.001

Table3 : Baseline characteristics of patients (Biochemical parameters).

Biochemical parameters	Whole population (n = 983)	VKAs (n = 291)	NOACs (n = 692)	p-Value
Albumin, g/dL	3.91 ± 0.36	3.90 ± 0.38	3.92 ± 0.34	0.42
Total cholesterol, mg/dL	167 ± 42	165 ± 41	168 ± 43	0.33
LDL cholesterol, mg/dL	100 ± 35	98 ± 34	101 ± 35	0.21
HDL cholesterol, mg/dL	51 ± 16	52 ± 16	51 ± 16	0.12
Triglycerides, mg/dL	100 (74–136)	95 (70–132)	101 (76–138)	0.05
Haemoglobin, g/dL	13.36 ± 1.51	13.68 ± 0.99	13.23 ± 1.67	<0.001
PLT, × 10^3/µL	219 ± 60	219 ± 60	218 ± 60	0.82
Na, mmol/L	141 (139–142)	141 (139–142)	141 (139–142)	0.21
K, mmol/L	4.4 (4.2–4.7)	4.5 (4.2–4.7)	4.4 (4.1–4.7)	0.012

Creatinine, mg/dL	1.05 ± 0.31	1.06 ± 0.35	1.05 ± 0.29	0.69
e-GFR, mL/min/1.73 m²	64 ± 18	64 ± 20	64 ± 17	0.98
Clearance creatinine, mL/min	68 ± 23	71 ± 24	67 ± 22	0.002
NT-proBNP, pg/mL	562 (512–1,357)	598 (523–1,737)	562 (489–1,356)	0.025
Fasting glucose, mg/dL	103 (95–119)	106 (99–113)	102 (94–126)	0.21
Fasting insulin, µU/mL	16.14 ± 6.62	15.85 ± 6.24	16.26 ± 6.78	0.37
HOMA index	4.22 (2.87–5.75)	3.90 (2.79–5.34)	4.32 (2.93–5.88)	0.046
Uric acid, mg/dL	5.5 (4.9–6.3)	5.4 (4.9–6.3)	5.5 (5.1–6.3)	0.41
AST, IU/L	20 (16–24)	19 (16–23)	20 (17–25)	0.0002
ALT, IU/L	19 (13–25)	17 (13–24)	19 (14–26)	0.013
Alkaline phosphatase, IU/L	78 (66–107)	76 (66–106)	78 (66–110)	0.20
GGT, IU/L	32 (21–42)	32 (19–42)	32 (21–42)	0.77

4.2 Conventional regression analysis

In the multivariable logistic regression model, treatment with a NOAC was independently associated with substantially lower odds of cognitive decline compared with VKA therapy. The estimated odds ratio was 0.322 (95% CI 0.221-0.469; $p < 0.0001$), corresponding to an approximate 67.8% relative reduction in the odds of decline in the NOAC group. This was the central inferential result of the clinical study and provided the first major indication that anticoagulant class might influence long-term cognitive trajectories in elderly AF.

Exploratory all-cause mortality analysis during follow-up did not identify a significant difference between treatment groups, suggesting that the cognitive findings were not trivially explained by a major survival imbalance alone. Although residual confounding cannot be excluded in an observational design, the consistency of the regression result encouraged deeper predictive exploration through machine learning.

4.3 Performance of the Random Forest model

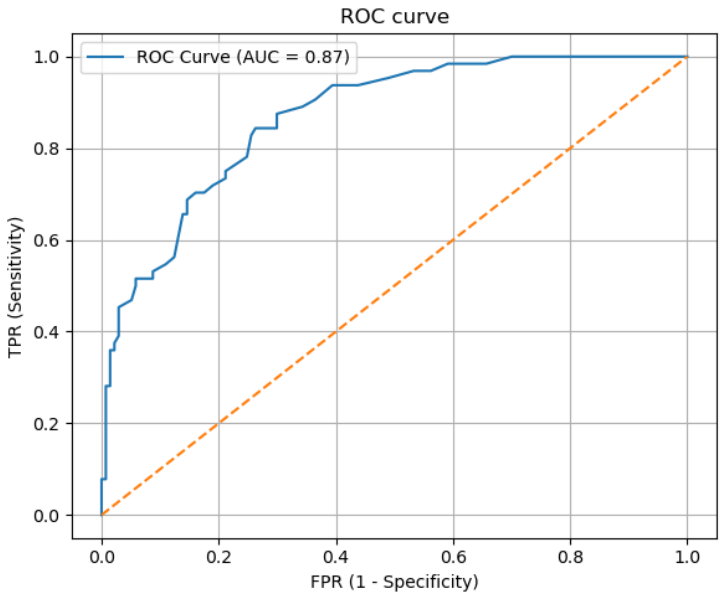
(figures 1-3)

The Random Forest classifier showed strong and stable discrimination. During repeated stratified cross-validation, the mean ROC AUC was approximately 0.8715 with a standard deviation of 0.0273, indicating both good discrimination and acceptable stability across resampled partitions. On the held-out test set, the class-weighted configuration achieved ROC AUC 0.880.

At the default decision threshold of 0.5, performance for the decline class reflected a typical trade-off seen in imbalanced medical datasets: precision was high (0.94), but recall was modest (0.47). In practical terms, when the model predicted cognitive decline it was usually correct, yet it missed a substantial fraction of true decline cases. A SMOTE-based alternative produced slightly lower ROC AUC (0.869) but improved recall to 0.53 with an F1-score around 0.62, while reducing precision to 0.74. Threshold optimization to 0.35 further increased recall to 0.84 and the F1-score to 0.68, at the cost of lower precision (0.57) and an overall accuracy of roughly 75%. The PR AUC was 0.763, supporting meaningful discrimination under class imbalance.

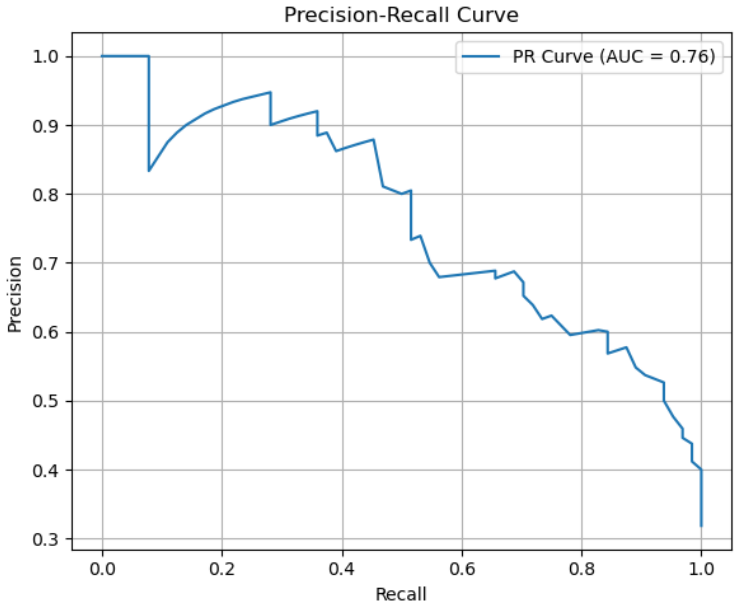
The confusion matrix at threshold 0.5 recorded 125 true negatives, 30 false negatives, 12 false positives, and 34 true positives. This distribution reinforces the interpretation that the unadjusted default threshold favored specificity more than sensitivity. In a research context centered on the early identification of vulnerable patients, the lower optimized threshold may therefore be clinically preferable.

Figure 1: Receiver Operating Characteristic (ROC) curve of the Random Forest model for the prediction of cognitive decline.



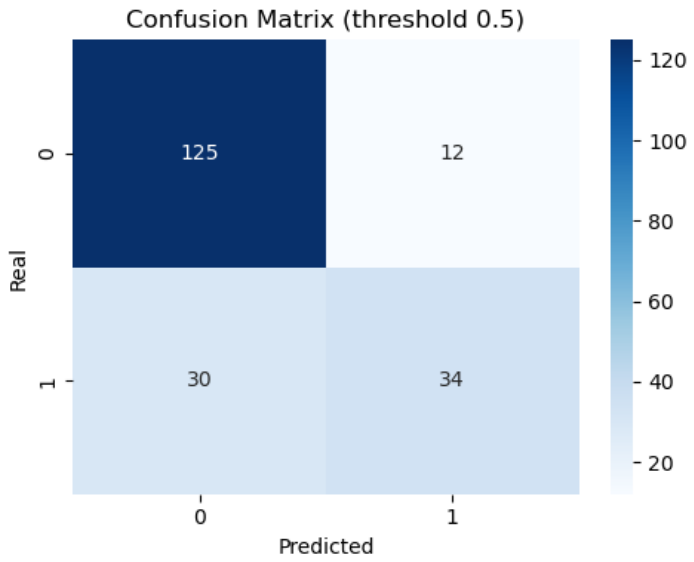
The graph illustrates the relationship between sensitivity (True Positive Rate) and 1-specificity (False Positive Rate). The Area Under the Curve (AUC) of 0.87 demonstrates the algorithm's high discriminative ability in distinguishing patients at risk, confirming the stability of the performance observed during stratified cross-validation. The dashed diagonal line represents the performance of a random classifier (AUC = 0.5).

Figure 2: Precision-Recall (PR) curve of the predictive model.



Unlike the ROC curve, PR analysis provides a more rigorous assessment of performance in the presence of class imbalance. The Area Under the Curve (AUC) of 0.76 indicates a good ability of the model to maintain acceptable precision even as sensitivity (recall) increases, confirming the algorithm's effectiveness in correctly identifying patients with cognitive decline while minimizing false positives.

Figure 3: Confusion matrix of the model on the test set (decision threshold = 0.5).



The matrix shows the distribution of predictions against the true labels. Along the main diagonal, the correct classifications are observed: 125 true negatives (class 0) and 34 true positives (class 1). However, the off-diagonal values reveal 30 false negatives (bottom left), indicating that, at the standard threshold, the model is highly specific (few false positives, n = 12) but poorly sensitive, failing to identify nearly half of the patients with cognitive decline.

4.4 Predicted probability distributions and feature importance

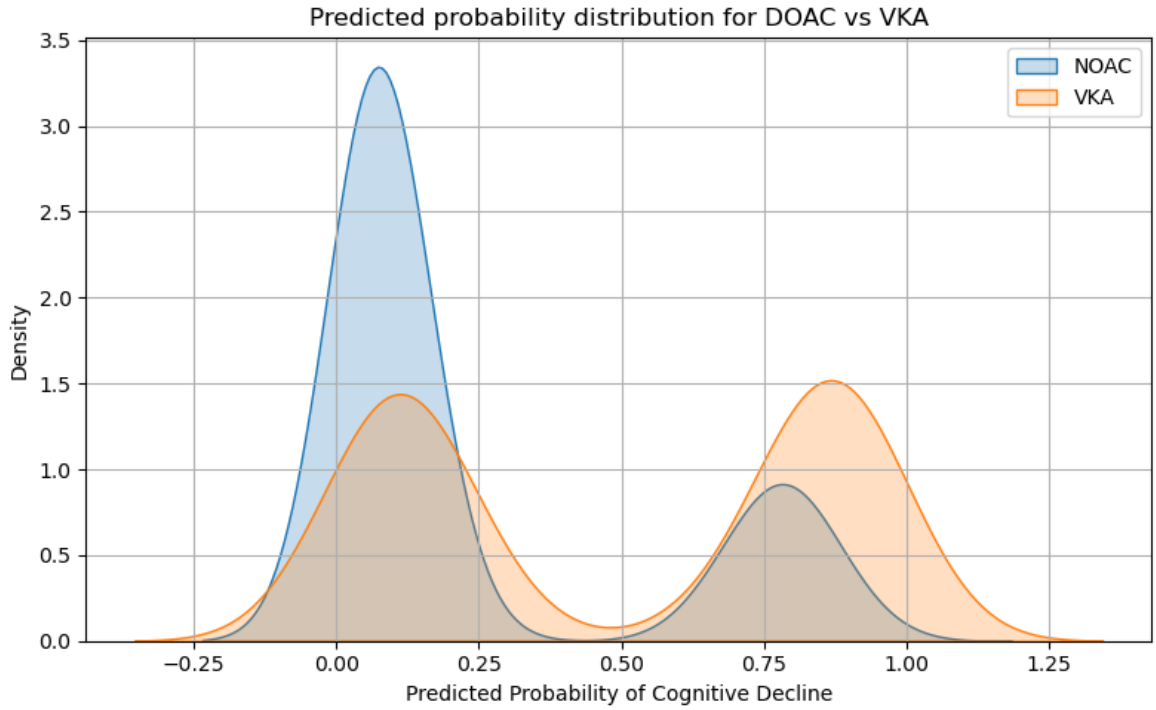
(figures 4-5)

Predicted probabilities of cognitive decline differed clearly according to anticoagulant class. Mean predicted probability was approximately 0.50 (SD 0.37) among VKA-treated patients and 0.24 (SD 0.30) among NOAC-treated patients. The Kolmogorov-Smirnov statistic of about 0.385 ($p < 0.001$) confirmed that these probability distributions were significantly different. Importantly, the divergence was observed at the level of the entire risk distribution and not only in a small subset of extreme predictions. This suggests that anticoagulant class had a pervasive influence within the predictive architecture of the model.

Permutation importance further clarified the hierarchy of predictors. Anticoagulant therapy emerged as the single most influential variable, with an average importance of about 0.042.

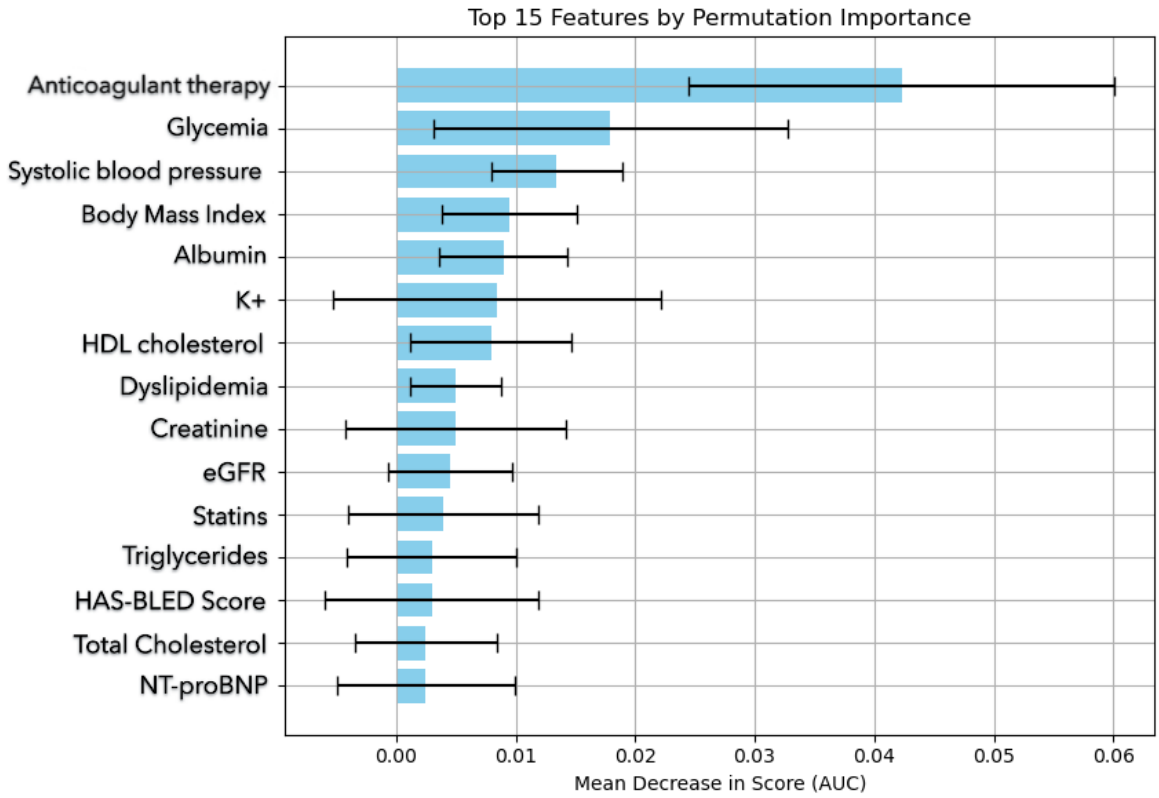
The next most informative features were glycemia (0.018), systolic blood pressure (0.013), body mass index (0.009), albumin (0.009), and potassium (0.008). This profile is clinically coherent. It indicates that cognitive decline in AF is shaped not only by treatment class but also by metabolic burden, hemodynamic stress, nutritional or inflammatory state, and broader cardiometabolic fragility.

Figure 4: Kernel Density Estimation (KDE) plot of the probabilities of cognitive decline predicted by the model



The distribution analysis shows a marked divergence between the treatment groups. The NOAC curve (blue) displays a pronounced peak at low probability values (between 0.0 and 0.25), indicating that the model assigns these patients a lower risk. In contrast, the VKA distribution (orange) shows a bimodal pattern with a substantial density concentrated at high probability values (> 0.75), confirming the association between vitamin K antagonists and a higher risk of cognitive deterioration.

Figure 5: Feature importance analysis (Permutation Importance)



The graph ranks the clinical variables according to their impact on the model's predictive performance, measured as the mean decrease in AUC following random permutation of feature values. The result confirms the research hypothesis: "Anticoagulant therapy" clearly emerges as the most influential predictor, carrying greater weight than traditional cardiovascular risk factors such as blood glucose, systolic blood pressure, and BMI. The black error bars indicate the variability in feature importance calculated across different iterations.

4.5 Results of the biomarker substudy

(table 4, figures 6-7)

The biomarker substudy enrolled 116 patients with acute ischemic stroke and 59 controls. Among the measured biomarkers, statistically significant between-group differences were demonstrated for OPN, PF4, and UCH-L1. Mean OPN values were 135.8 ± 96.1 in AIS patients versus 92.1 ± 52.6 in controls ($p = 0.002$). PF4 values were 220 ± 176 versus 102.4 ± 85 ($p < 0.0001$), and UCH-L1 values were 826 ± 360 versus 555 ± 195 ($p < 0.0001$). The combined logistic model including PF4, OPN, and UCH-L1 achieved an AUC of 0.827.

These data indicate that acute cerebrovascular events occurring within the broader AF trajectory are accompanied by a measurable thrombo-inflammatory and neuroglial signal. PF4 reflects platelet activation and thrombogenic activity, OPN captures inflammatory remodeling and cellular recruitment, and UCH-L1 reflects neuronal injury. Their combined performance supports the view that stroke in this setting is not a purely hemodynamic or embolic event but a biologically layered syndrome involving coagulation, inflammation, endothelial damage, and neural tissue injury. In the context of the thesis, this substudy strengthens the plausibility of linking long-term cognitive risk to event-level molecular pathways.

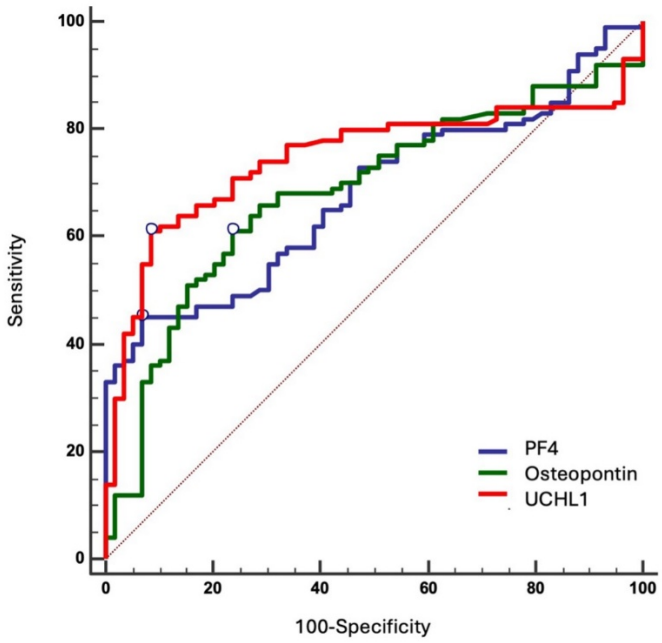
Table 4: Comparison of demographic characteristics, cardiovascular risk factors, ongoing therapies, and circulating laboratory biomarkers between controls and patients.

Variables	**Controls**	**Patients**	**p-value**
Number	59	116	
Sex			0.896
Female	24	46	
Male	35	70	
Age, years	67.7 ± 10.7	70.8 ± 11.9	0.104
Systolic blood pressure, mmHg	134.4 ± 21.3	144.5 ± 20.5	0.003
Diastolic blood pressure, mmHg	73.5 ± 14.4	78.9 ± 13.2	0.014
Hypertension, n	15	104	<0.0001
Dyslipidemia, n	18	63	0.003
Diabetes, n	18	54	0.05
Smoking, n	6	41	0.001
Atrial fibrillation, n	16	32	0.893
Therapy			

Antiplatelet agents, n	10	53	<0.0001
Warfarin, n	6	16	0.519
DOACs, n	14	21	0.349
Heart rate	77.2 ± 13.2	76.9 ± 12.6	0.881
BMI	27 ± 6.7	27 ± 5.1	0.834
C-reactive protein	16 ± 36.2	20 ± 26.1	0.423
ESR	17 ± 19.3	17 ± 12.3	0.861
Total cholesterol	171 ± 34	170 ± 50	0.944
LDL cholesterol	87 ± 29	93 ± 31	0.152
Triglycerides	120 ± 51	131 ± 49	0.2
PCR	0.52 ± 0.39	0.52 ± 0.43	0.91
ACR	0.21 ± 0.19	0.41 ± 0.56	0.017
OPN	92.1 ± 52.6	135.8 ± 96.1	0.002
IP-10, pg/mL	231 ± 241	266 ± 262	0.397
sCD141, ng/mL	9.2 ± 5	9 ± 5.3	0.836
PF4, ng/mL	102.4 ± 85	220 ± 176	<0.0001
GFAP, ng/mL	0.35 ± 0.34	0.32 ± 0.63	0.768
FABP3, pg/mL	258 ± 216	360 ± 780	0.328
UCHL1, µg/mL	555 ± 195	826 ± 360	<0.0001

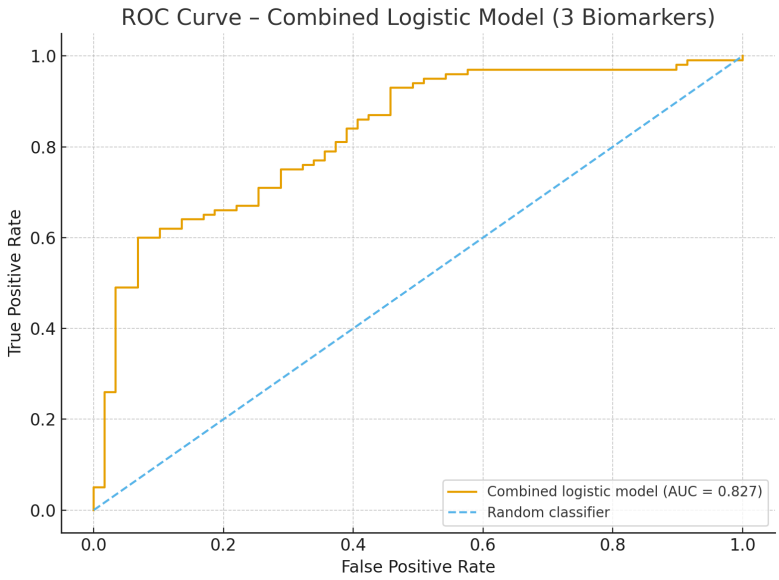
List of abbreviations: ACR = albumin-to-creatinine ratio; BMI = body mass index; DOACs = direct oral anticoagulants; ESR = erythrocyte sedimentation rate; FABP3 = fatty acid-binding protein 3; GFAP = glial fibrillary acidic protein; IP-10 = interferon gamma-induced protein 10; LDL = low-density lipoprotein; OPN = osteopontin; PCR = protein-to-creatinine ratio; PF4 = platelet factor 4; sCD141 = soluble CD141; UCHL1 = ubiquitin C-terminal hydrolase L1.

Figure 6: ROC curves with AUC values for each of the three biomarkers showing the best diagnostic performance when considered individually



List of abbreviations: **ROC**: receiver operating characteristic; **AUC**: area under the curve; **PF4**: platelet factor 4; **UCHL1**: ubiquitin carboxyl-terminal hydrolase L1

Figure 7: ROC curve with AUC of the multimarker model combining the three biomarkers PF4, OPN, and UCHL1.



List of abbreviations: **ROC**: receiver operating characteristic; **AUC**: area under the curve; **PF4**: platelet factor 4; **UCHL1**: ubiquitin carboxyl-terminal hydrolase L1

5. Discussion

5.1 Main findings

The present thesis integrates a longitudinal clinical dataset with a mechanistic biomarker framework and yields a coherent message. In an elderly multicenter cohort with non-valvular AF, NOAC therapy was associated with significantly lower odds of cognitive decline than VKA treatment. This result was observed in multivariable regression and was mirrored by machine-learning outputs, where anticoagulant therapy emerged as the most influential predictor of decline. At the same time, the biomarker substudy identified a biologically plausible acute signature of stroke-related injury based on thrombo-inflammatory and neuroglial markers. The overall picture is therefore internally consistent across inferential statistics, predictive modeling, and molecular profiling.

5.2 Interpreting the association between anticoagulant class and cognition

Why might NOAC therapy be associated with better preservation of cognition? The most straightforward explanation is more stable protection from recurrent embolic injury. VKA efficacy in routine care is critically dependent on maintaining adequate therapeutic range, and fluctuations in anticoagulant intensity may expose patients to alternating ischemic and hemorrhagic risk. In contrast, NOACs provide a more predictable anticoagulant effect, fewer interactions, and lower rates of intracranial bleeding in several contexts [27-28]. Over years of exposure, these advantages may translate into lower cumulative burden of overt stroke, silent infarction, or microhemorrhagic injury.

A second explanation concerns treatment complexity. Elderly patients often struggle with fluctuating diet, polypharmacy, frailty, renal function changes, and variable healthcare access. Under such conditions, the practical simplicity of NOAC therapy may improve treatment consistency. This may not be fully captured by standard baseline variables but

could still influence cerebral outcomes longitudinally. A third possible mechanism is indirect organ protection. Some studies suggest that DOACs may have a more favorable impact on renal function over time than VKAs [29]. Because renal dysfunction is tightly linked to vascular stiffness, endothelial injury, uremic toxicity, and cognitive decline, this indirect pathway may contribute to a broader neuroprotective effect.

At the same time, caution is required. Observational data cannot fully exclude confounding by indication. In the present cohort, baseline differences between treatment groups were substantial in several domains, including age, prior vascular disease, and concomitant therapies. Although multivariable adjustment and machine-learning modeling reduce some of this concern, they do not establish causality. The present findings therefore support a strong clinical association rather than a definitive causal conclusion.

5.3 Why Random Forest performed well in this setting

The predictive task in this thesis is particularly suitable for a Random Forest approach. Cognitive decline in elderly AF is unlikely to result from a single biological axis. Instead, it emerges from complex interactions among age, vascular burden, diabetes, blood pressure, renal status, nutritional state, arrhythmia phenotype, and treatment. Random Forest naturally accommodates such complexity. It handles continuous and categorical data without strong distributional assumptions, captures nonlinear effects, and remains relatively resistant to overfitting when coupled with appropriate validation [35,37].

The cross-validated ROC AUC around 0.87 and the held-out ROC AUC of 0.88 indicate a model with strong discrimination. The more nuanced finding lies in the trade-off between precision and recall. At threshold 0.5, the model was highly precise but insufficiently sensitive for the minority decline class. This is not a weakness of the algorithm alone; it reflects a common tension in clinical prediction when the positive event is relatively infrequent. The improvement in recall after SMOTE and threshold optimization is therefore

clinically meaningful. If the purpose of the model is to flag patients for closer monitoring or preventive intensification, missing fewer true decline cases may be more important than maintaining very high precision.

The feature-importance analysis is equally instructive. Anticoagulant therapy did not simply appear as one variable among many; it ranked clearly first. The next predictors—glycemia, systolic blood pressure, BMI, albumin, potassium—outline a recognizable phenotype of cardiometabolic and systemic vulnerability. Thus, the model supports a view of cognitive decline in AF as an interaction between treatment-related factors and the wider frailty-metabolic axis.

5.4 Relationship between the clinical findings and the biomarker substudy

The molecular substudy provides an important translational layer to the thesis. Elevated PF4 indicates heightened platelet activation and thrombo-inflammatory signaling. Increased OPN suggests active inflammatory remodeling and leukocyte recruitment, whereas elevated UCH-L1 reflects neuronal injury. Their combined AUC of 0.827 suggests that these processes, taken together, offer meaningful discriminatory information in acute ischemic stroke.

This is relevant for the longitudinal AF cohort because it supports the notion that cognitive decline may be fueled by repeated or clinically silent episodes along the same biological continuum. A patient may never experience a large disabling stroke, yet may still be exposed to recurrent low-grade thrombo-inflammatory injury, endothelial dysfunction, and subtle neuroglial damage. The biomarker results therefore do not stand apart from the main study; rather, they lend biological plausibility to the broader hypothesis that AF-related cognitive decline reflects cumulative interaction between vascular events and systemic injury pathways.

In translational terms, this opens the possibility of future models that combine longitudinal clinical features with event-related or baseline biomarker data. Such integration could improve risk stratification, identify mechanistic subphenotypes, and eventually support more personalized treatment decisions.

5.5 Comparison with the literature

The present findings are broadly consistent with the literature suggesting that AF is associated with cognitive impairment independently of clinically apparent stroke [16-20,23-25]. They also align with studies reporting benefit from anticoagulation in relation to dementia risk and with reports suggesting more favorable long-term cognitive trajectories among NOAC-treated patients than among VKA-treated patients [27,29-30]. At the same time, they should be interpreted within the broader debate, because not all observational analyses have shown a clear advantage of NOACs over well-managed warfarin, and residual confounding remains a recurrent issue.

The study also fits with contemporary work on the heart-brain axis and on the expanding role of machine learning in cardiovascular and stroke medicine [14,33,36]. In recent years, prediction research has moved from asking whether clinical scores are useful to asking how high-dimensional datasets can be translated into practical risk tools. The present thesis contributes to this direction by showing that machine learning can add value without displacing conventional regression, provided that the modeling choices remain clinically grounded and transparently reported.

5.6 Strengths and limitations

This work has several strengths. It is based on a multicenter elderly cohort, reflects real-world clinical practice, and combines conventional multivariable analysis with a supervised machine-learning framework. The internal coherence across logistic regression, Random Forest performance, predicted risk distributions, and permutation importance strengthens the

credibility of the central finding. The incorporation of a biomarker substudy adds translational depth and moves the thesis beyond a purely statistical exercise.

Important limitations must also be acknowledged. The design is observational and therefore vulnerable to confounding by indication and unmeasured bias. The cognitive outcome relied on MMSE, a pragmatic but not domain-specific tool. Neuroimaging data were not available in a standardized serial manner for all cohort participants, limiting direct quantification of silent infarction or small-vessel disease. External validation of the machine-learning model was not available within the present work. Finally, the biomarker substudy, although informative, remains event-centered and relatively modest in size.

These limitations do not negate the findings, but they define the appropriate level of inference. The thesis should be viewed as strong evidence for a clinically meaningful association and for the feasibility of machine-learning risk modeling in AF-related cognitive decline, while leaving room for future prospective validation and mechanistic refinement.

5.7 Clinical implications and future perspectives

The clinical implications of this thesis are potentially significant. Cognitive preservation should become an explicit therapeutic objective in AF management. When treatment options are otherwise appropriate, the possibility that anticoagulant class may influence long-term cognition deserves attention, especially in older adults at high vascular and neurocognitive risk. Moreover, risk stratification for AF should move beyond stroke and bleeding alone. The patient who is clinically stable today may still be accumulating silent brain injury that will manifest as cognitive decline years later.

Future research should proceed along several lines. First, external validation of the Random Forest model is necessary to test generalizability. Second, calibration and decision-curve analyses would help define its practical clinical utility. Third, serial neuroimaging could clarify how the predicted risk relates to silent infarcts, microbleeds, and atrophy. Fourth, the

biomarker framework should be expanded to include larger prospective samples and possibly repeated measurements. Finally, combined models incorporating clinical variables, laboratory data, imaging, and digital-health signals may ultimately provide a richer and more individualized approach to AF-related brain risk.

6. Conclusions

This doctoral thesis supports the concept that atrial fibrillation is not only an arrhythmia to be managed for symptoms and stroke prevention, but also a long-term determinant of brain health. In an elderly multicenter cohort, NOAC therapy was associated with a markedly lower risk of cognitive decline than VKA treatment, and this association remained central across both conventional regression and Random Forest modeling. The predictive model showed robust discrimination and identified anticoagulant therapy as the most influential feature within a broader network of cardiometabolic and biochemical predictors.

The biomarker substudy complements these findings by demonstrating that acute ischemic stroke in this clinical context is accompanied by a measurable thrombo-inflammatory and neuroglial signature, particularly involving PF4, OPN, and UCH-L1. Together, the clinical and molecular results support an integrated interpretation in which AF-related cognitive decline emerges from the cumulative interaction of embolic risk, perfusion instability, vascular dysfunction, systemic inflammation, and treatment-related factors.

The central message of the thesis is therefore clear: cognitive outcomes deserve to be considered a core endpoint in AF management. Machine-learning tools can assist this effort by capturing complex multidimensional risk patterns, but their value depends on rigorous validation and clinically meaningful implementation. The present work offers a foundation for that next step and argues for a more comprehensive, brain-conscious, and precision-oriented approach to the care of patients with atrial fibrillation.

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