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Anticoagulation in Device-Detected Atrial Fibrillation: Reconciling Arrhythmia Burden, Clinical Stroke Risk, and Treatment Benefit

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Abstract

Implanted rhythm devices increasingly identify atrial high-rate episodes (AHREs) and subclinical atrial fibrillation (AFib) in patients without previously documented clinical AFib. Their thromboembolic implications are clinically important, but arrhythmia burden alone has not been validated as a threshold for anticoagulation. This critical narrative review evaluates observational risk associations, the ARTESiA and NOAH-AFNET 6 randomized trials, subsequent subgroup analyses, and decision models, distinguishing predictors of stroke risk from predictors of treatment benefit. ARTESiA found that apixaban reduced stroke or systemic embolism relative to aspirin while increasing major bleeding, especially gastrointestinal bleeding; differences in intracranial and fatal bleeding were not statistically significant. NOAH-AFNET 6 did not demonstrate a statistically significant reduction in its broader primary efficacy composite with edoxaban and found more all-cause death or major bleeding. A study-level meta-analysis of these same two trials showed reduced ischemic stroke (relative risk 0.68, 95% confidence interval 0.50–0.92) and increased major bleeding (1.62, 1.05–2.50), without a demonstrated mortality benefit. Observational studies associate greater AF exposure with thromboembolism, whereas an ARTESiA analysis found no significant association between selected baseline episode measures and subsequent stroke or modification of apixaban benefit. Clinical characteristics, including previous stroke or transient ischemic attack, may identify higher absolute-risk groups, but subgroup results have not established validated treatment-selection cutoffs. Estimates of net clinical benefit and cost-effectiveness also depend on patient selection, event severity, time horizon, and model assumptions. Current decisions should distinguish confirmed rhythm diagnoses, individualized absolute risks, bleeding susceptibility, and patient preferences while acknowledging unresolved uncertainty.

Keywords: Anticoagulation; Atrial fibrillation (AFib); Atrial high-rate episodes; Bleeding; Device-detected atrial fibrillation; Risk stratification; Stroke; Subclinical atrial fibrillation; Thromboembolism.

Introduction: A Clinically Important Decision Without a Validated Threshold

Pacemakers, implantable cardioverter-defibrillators, resynchronization devices, and implantable monitors increasingly identify atrial arrhythmias outside episodic, symptom-driven electrocardiography. A device-detected atrial high-rate episode (AHRE) is initially an algorithmic detection of rapid atrial activity; the underlying electrogram may show atrial fibrillation (AFib),

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another atrial tachyarrhythmia, oversensing, or artifact. Electrogram-adjudicated subclinical AF (SCAF) is therefore more specific than an unverified AHRE, and prior ECG-documented clinical AF represents a different diagnostic and therapeutic context. A 2025 consensus statement defines AF burden primarily as the percentage of a specified monitoring interval spent in AF and recommends also reporting the longest uninterrupted episode where appropriate [1]. Anticoagulation has established benefits in appropriately selected patients with ECG-documented AF; these cannot be directly transferred as identical absolute benefits to patients with brief device-detected episodes. The 2023 US and 2024 European guidelines incorporate clinical thromboembolic risk, episode characteristics, bleeding susceptibility, and shared decision-making, but express different degrees of specificity regarding treatment thresholds [2,3]. The central clinical question is not solely whether an episode predicts stroke, but whether anticoagulation prevents enough clinically consequential events in a particular patient to justify bleeding risk and treatment burden [4-15].

Evidence identification: PubMed and Elsevier Embase were searched on 17 October 2026 using terms for device-detected or subclinical atrial fibrillation, atrial high-rate episodes, anticoagulation, stroke, thromboembolism, and bleeding. The searches returned 800 PubMed citations and 2,225 Embase article records; 141 Embase trial-registry entries were evaluated separately. Records were deduplicated and preliminarily prioritized using titles and abstracts. Full-text appraisal focused on influential randomized and observational studies, relevant secondary analyses, and decision models, with additional references identified from trial appendices, guidelines, and citation lists. This was a structured search supporting a critical narrative review, not a formal systematic review: study selection was not independently duplicated and exhaustive full-text screening was not undertaken. We critically examine AF-burden observations, the two principal randomized anticoagulation trials, overlapping secondary analyses, and published clinical and economic models. Three noninterchangeable questions organize the review: Which measurements predict untreated stroke risk? Which characteristics have been shown to modify the relative treatment effect? How do these findings translate into absolute benefits and harms over a specified time horizon? The synthesis does not constitute an independent quantitative meta-analysis.

Definitions, Diagnostic Confirmation, and A Mechanistic Framework

AHREs are automated detections of rapid atrial activity, not proof of AF in every instance. Available stored electrograms should be reviewed to adjudicate rhythm type and episode duration; devices can misclassify other atrial tachyarrhythmias, noise, and oversensing. A photoplethysmography-only notification from a consumer device does not establish the same rhythm phenotype as an adjudicated implanted-device electrogram. Established ECG-documented AF should be explicitly distinguished from device-detected episodes in applying the anticoagulation evidence and guideline recommendations [1,2]. Across the literature, "AF burden" is used for several distinct exposure measures. The ESC/EHRA consensus proposes the proportion of monitored time spent in AF, reported as a percentage together with the monitoring duration, as the primary standardized definition. It also encourages the duration of the longest uninterrupted episode as a complementary measure. Episode counts, maximal daily duration, longest single episode, and cumulative AF time are analytically different and depend on observation window, device technology, and monitoring completeness. These quantities must not be treated as interchangeable in prognostic or treatment-effect analyses [1]. Potential thromboembolism involves interacting rhythm-related and atrial-substrate mechanisms. During AF, impaired coordinated atrial contraction and reduced left atrial appendage emptying may promote blood stasis. In parallel, atrial cardiomyopathy can involve myocyte and extracellular-matrix remodeling, interstitial fibrosis, altered conduction, and persistent contractile dysfunction. Inflammatory and endothelial processes and common conditions such as hypertension, diabetes, and heart failure may contribute to this substrate. An international electrophysiology consensus describes atrial cardiomyopathy in terms of structural, architectural, contractile, and electrophysiological changes [16]. These pathways offer biological plausibility for AF acting both as an intermittent contributor and as a marker of thromboembolic risk. They do not establish that an individual episode caused a particular stroke, that the absence of recent device-detected AF implies safety, or that any atrial substrate measure predicts anticoagulation treatment benefit.

Natural History and Observational Relationships with Stroke

The ASSERT duration analysis included 2,455 device recipients without prior clinical AF after its specified exclusions. A longest SCAF episode >24 hours was associated with stroke or systemic embolism (adjusted hazard ratio [HR] 3.24; 95% confidence interval [CI] 1.51–6.95), whereas durations of 6 minutes to 24 hours did not show a statistically significant difference from no SCAF [17]. TRENDS measured the greatest daily atrial tachyarrhythmia burden within the preceding 30 days; compared with no detected burden, a high-burden category around 5.5 hours had an adjusted HR of 2.20 (95% CI 0.96–5.05; P=.06), a suggestive but statistically inconclusive association [18]. KP-RHYTHM studied a different population with established paroxysmal AF; among 1,965 participants, the highest

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monitored-burden tertile (≥11.4% of recorded time) was associated with thromboembolism while off anticoagulation (CHA_2DS_2-VASc-adjusted HR 3.16; 95% CI 1.51–6.62). This does not establish a device-detected SCAF treatment threshold [19].

Observational associations describe prognosis, not modification of the randomized effect of anticoagulation. Confounding by vascular comorbidity, indication for device implantation, antithrombotic exposure, and monitoring methods requires attention. In a temporal ASSERT analysis, 26 of 51 patients with stroke or systemic embolism had SCAF documented at some time; 18 had SCAF before the event, but only 4 of all 51 (8%) had an episode detected during the preceding 30 days [20]. This temporal separation challenges a simplistic immediate-trigger explanation without establishing that AF is merely incidental. In the LOOP randomized trial, implantable-loop-recorder screening increased AF detection (31.8% vs 12.2%) and anticoagulation initiation (29.7% vs 13.1%) but did not significantly reduce stroke or systemic embolism compared with usual care (HR 0.80; 95% CI 0.61–1.05; P=.11). LOOP evaluated a screening-and-treatment strategy, not anticoagulation versus no anticoagulation among an already-confirmed SCAF population [21]. Episode burden, incident ECG-documented AF, and stroke and bleeding risk factors can evolve during longitudinal follow-up [3]. A single baseline device interrogation may therefore incompletely describe future exposure. Reassessment after changes in documented rhythm or clinical risk is reasonable, but the observational evidence above does not establish that burden-triggered discontinuation and reinitiation of anticoagulation is safe. A subsequent ARTESiA analysis of arrhythmia progression adds longitudinal context: during an extended mean 4.1-year follow-up, 1,250 of 4,012 participants (31.2%) progressed to clinical AF or a subclinical episode >24 hours, an incidence of 9.3% per patient-year. Progression was associated with all-cause mortality (time-dependent adjusted HR 2.12, 95% CI 1.83–2.45), but not with a significantly greater rate of stroke/systemic embolism after accounting for antithrombotic strategy as a time-dependent covariate (HR 1.03, 95% CI 0.67–1.57). Six baseline predictors discriminated progression only modestly (C statistic 0.59). These are within-trial observational comparisons following a change in AF phenotype, not a randomized test of initiating anticoagulation at progression [22].

Artesia and Noah-Afnet 6: Design Differences Before Outcome Differences

NOAH-AFNET 6 randomized 2,608 patients aged ≥65 years, of whom 2,536 patients were included in the primary modified intention-to-treat analysis. The 2,536 patients has a device-detected atrial high-rate episode (AHRE) ≥6 minutes, at least one additional stroke-risk factor, and no ECG-documented AF. No upper AHRE-duration limit was imposed. Edoxaban was compared with a control strategy of placebo or aspirin when indicated (53.9% had an aspirin indication at randomization). Median follow-up was 21 months. The trial was stopped early because of safety concerns and an independent, informal futility assessment, limiting precision for individual stroke outcomes. Its primary efficacy composite comprised cardiovascular death, stroke, or systemic embolism; the safety composite comprised all-cause death or major bleeding [23]. ARTESiA randomized 4,012 patients with device-detected subclinical AF (SCAF) lasting ≥6 minutes but <24 hours and elevated clinical stroke risk to apixaban or aspirin 81 mg daily. Mean follow-up was 3.5 years. The primary efficacy endpoint was stroke or systemic embolism. If SCAF >24 hours or clinical AF developed, blinded therapy was stopped and open-label anticoagulation initiated or recommended; the primary efficacy analysis censored follow-up at that transition. The prespecified headline major-bleeding assessment was on-treatment, whereas other bleeding results used different follow-up definitions. The trial accrued fewer primary efficacy events than planned [24]. The trials addressed related but nonidentical questions: AF confirmation and duration criteria, comparison treatments, follow-up, AF-progression management, and primary endpoint definitions differed. In NOAH-AFNET 6 the systemic-embolism category additionally included myocardial infarction and pulmonary embolism; ARTESiA used a narrower stroke/systemic-embolism endpoint. Comparing significance levels from these dissimilar primary composites cannot establish heterogeneity in anticoagulation efficacy. Nor can annual stroke rates from one analysis be mechanically subtracted from bleeding rates measured under different censoring rules. Table 1 identifies the study-level constraints most consequential for interpretation.

Randomized Efficacy, Bleeding, Mortality, and Compatible Inference

ARTESiA demonstrated a lower rate of stroke or systemic embolism with apixaban than aspirin (0.78% vs 1.24% per patient-year; HR 0.63, 95% CI 0.45–0.88). Its headline on-treatment major-bleeding analysis yielded rates of 1.71% vs 0.94% per patient-year (HR 1.80, 95% CI 1.26–2.57). In the trial's separately reported intention-to-treat analysis with AF-progression censoring, major bleeding was 1.53% vs 1.12% per patient-year (HR 1.36, 95% CI 1.01–1.82). In supplementary intention-to-treat analyses without censoring after clinical AF or SCAF >24 hours, the stroke/systemic-embolism HR was 0.70 (95% CI 0.51–0.96) and the major-bleeding HR was 1.36 (95% CI 1.04–1.79) [24]. The two HRs of 1.36 derive from different analysis specifications and must not be treated as a single interchangeable estimate. A prespecified ARTESiA analysis further characterized major-bleeding sites and severity in 3,961 participants who received study

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Table 1: Trial design and analysis map.

Feature	ARTESiA [24]	NOAH-AFNET 6 [23]
Randomized participants	4,012 (apixaban n=2,015; aspirin n=1,997)	Out of randomized 2,608 patients, 2,536 patients were included in the primary modified intention-to-treat analysis (edoxaban n=1,270; control n=1,266)
Device rhythm eligibility	Confirmed SCAF ≥6 min to <24 h	AHRE ≥6 min; no maximum episode duration
Study treatment / comparator	Apixaban / aspirin 81 mg daily	Edoxaban / placebo or aspirin when indicated (~54%)
Follow-up	Mean 3.5 years	Median 21 months
Primary efficacy endpoint	Stroke or systemic embolism	CV death, stroke, or systemic embolism (includes MI/PE within systemic embolism definition)
Primary efficacy HR (95% CI)	0.63 (0.45–0.88)	0.81 (0.60–1.08)
Headline safety (primary)	On-treatment major bleeding HR 1.80 (1.26–2.57)	All-cause death or major bleeding HR 1.31 (1.02–1.67)
Study limitation	Progression-censored efficacy; headline bleeding on-treatment; fewer endpoints than planned	Premature stopping; different primary composite; sparse ischemic strokes
Ischemic stroke, secondary	HR 0.62 (0.43–0.91)	HR 0.79 (0.45–1.39)
Major bleeding, ITT-type	HR 1.36 (1.01–1.82), progression-censored	HR 2.10 (1.30–3.38), major-bleeding component
Supplementary sensitivity	Without progression censoring: stroke/SE HR 0.70 (0.51–0.96)	Without censoring at unblinding/ECG AF: composite efficacy HR 0.81 (0.62–1.06)

Note: Trials differed in entry criteria, comparator, primary composites, time to follow-up, and censoring. Efficacy and safety estimates are not harmonized for simple subtraction. CV, cardiovascular; AF, atrial fibrillation; AHRE, atrial high-rate episode.

treatment. Gastrointestinal major bleeding was more frequent with apixaban than aspirin (0.89 vs 0.40 per 100 patient-years; HR 2.23, 95% CI 1.32–3.78). Intracranial bleeding (0.33 vs 0.40 per 100 patient-years; HR 0.82, 95% CI 0.43–1.57) and fatal bleeding (0.10 vs 0.16 per 100 patient-years; HR 0.63, 95% CI 0.20–1.91) were not statistically different; these confidence intervals do not demonstrate equivalence or exclude clinically relevant differences. Most index major bleeding events were non emergencies characterized by hemoglobin decline. Associations of major bleeding with NSAID use, cancer and age were identified within the treated cohort and should not be interpreted as randomized causal effects. This report is a secondary analysis of ARTESiA rather than additional trial participants [25]. NOAH-AFNET 6 did not demonstrate a statistically significant reduction in its broader primary efficacy composite of cardiovascular death, stroke, or systemic embolism (3.2% vs 4.0% per patient-year; HR 0.81, 95% CI 0.60–1.08). Ischemic stroke alone was uncommon (0.9% vs 1.1% per patient-year; HR 0.79, 95% CI 0.45–1.39), and the confidence interval does not exclude clinically important benefit or harm. The primary all-cause death/major-bleeding safety composite increased with edoxaban (5.9% vs 4.5% per patient-year; HR 1.31, 95% CI 1.02–1.67); major bleeding considered separately increased (2.1% vs 1.0% per patient-year; HR 2.10, 95% CI 1.30–3.38). In a sensitivity analysis without censoring at unblinding or ECG-documented AF, the primary efficacy composite remained nonsignificant (HR 0.81, 95% CI 0.62–1.06) [23]. These findings concern different primary endpoints from ARTESiA and do not independently disprove ischemic-stroke prevention. The published study-level meta-analysis combined the same two randomized trials (6,548 participants): ischemic stroke RR 0.68 (95% CI 0.50–0.92; I^2=0%) and major bleeding RR 1.62 (95% CI 1.05–2.50; I^2=61%) [26]. Using pooled trial-based comparator rates, the authors estimated approximately 3 fewer ischemic strokes and 7 more major bleeds per 1,000 patient-years; these unweighted counts do not constitute a patient-specific net-benefit index. Neither cardiovascular nor all-cause mortality was significantly lower with anticoagulation. For major bleeding, the primary synthesis relied principally on intention-to-treat-type results because NOAH-AFNET 6 did not supply comparable on-treatment outcomes; the meta-analysis is not a third independent trial. Heterogeneity statistics derived from only two trials are imprecise and should not be interpreted as proof of homogeneity. Accordingly, ARTESiA's statistically significant primary result and NOAH-AFNET 6's nonsignificant broader composite do not imply opposite effects on ischemic stroke. Pooled evidence supports ischemic-stroke prevention with apixaban or edoxaban in the studied device-detected AF populations while identifying increased major bleeding. Generalization to all brief episodes, other anticoagulants, wearable alerts, or a universal treatment policy would exceed the randomized evidence [23,24,26].

Clinical Stroke-Risk Phenotypes: Greater Absolute Benefit Without Proven Relative-Effect Modification

In ARTESiA participants with CHA_2DS_2-VASc >4, annual stroke/systemic-embolism rates were 0.98% with apixaban and 2.25% with aspirin; annual major-bleeding rates

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were 2.13% and 1.45%, respectively [27]. At 3.5 years, the estimated cumulative difference was 3.95 percentage points fewer strokes/systemic emboli (95% CI 1.19–6.72), alongside 1.70 percentage points more major bleeding (95% CI −1.25 to 4.66). The 1.28 fewer stroke/systemic-embolism events and 0.68 more major bleeds per 100 patient-years derived from annual rates are distinct quantities from these cumulative-incidence contrasts. Relative treatment-effect interactions across CHA_2DS_2-VASc strata were nonsignificant for stroke/systemic embolism (P=0.23) and major bleeding (P=0.91); the absolute stroke-reduction interaction was suggestive but nonsignificant (P=0.06). These subgroup results should not be promoted to a validated threshold at score >4. A complementary prespecified NOAH-AFNET 6 subgroup analysis evaluated 741 participants with CHA_2DS_2-VASc >4. The trial's broad efficacy composite (cardiovascular death, stroke, or systemic embolism) occurred in 33/361 edoxaban-treated patients (4.6 per 100 patient-years) and 37/380 controls (5.3 per 100 patient-years; HR 0.88, 95% CI 0.55–1.41). The composite of all-cause death or major bleeding occurred in 62/361 (8.7 per 100 patient-years) versus 39/380 (5.6 per 100 patient-years; HR 1.59, 95% CI 1.06–2.39). The ischemic-stroke rate alone remained approximately 1.2–1.3 per 100 patient-years in this higher-score stratum. Across the full CHA_2DS_2-VASc distribution, treatment interactions were nonsignificant for both the efficacy composite (P=0.57) and safety composite (P=0.34). In exploratory multivariable analyses, older age, diabetes and lower eGFR predicted the broader efficacy composite—not necessarily isolated ischemic stroke—whereas older age, heart failure, diabetes, prior stroke and lower eGFR predicted the safety composite. Subgroup power was limited and multiplicity was not adjusted; this reuse of the NOAH-AFNET 6 population must not be treated as another trial. Its endpoints, comparator and follow-up differ from ARTESiA, precluding a direct comparison of absolute subgroup benefit [28]. In a prespecified ARTESiA subgroup analysis, 346 patients with prior stroke or transient ischemic attack (TIA) experienced annual stroke/systemic-embolism rates of 1.20% with apixaban versus 3.14% with aspirin. At 3.5 years, the estimated cumulative absolute reduction was 7 percentage points (95% CI 2–12), with a 3-point excess of major bleeding (95% CI −1 to 8). Among participants without prior stroke/TIA, the corresponding stroke/systemic-embolism reduction was approximately 1 point [29]. The interaction for relative treatment effect was not statistically significant (P=0.24); the interaction for cumulative absolute difference (P=0.03) was tested post hoc, without multiplicity adjustment. These results suggest a possible greater absolute benefit with high baseline risk, not established differences in the relative drug response. The corresponding NOAH-AFNET 6 secondary analysis included 253 participants with prior stroke/TIA: 4/122 assigned to edoxaban and 6/131 controls experienced stroke, whereas major bleeding occurred in 8/122 and 2/131, respectively [30]. No significant treatment interaction by prior stroke/TIA was identified, and event counts were small. This comparison with ARTESiA is qualitative, not a valid cross-trial calculation of subgroup treatment heterogeneity, because anticoagulants, comparators, endpoints, and follow-up differed. A combined secondary analysis of the two randomized trials associated vascular disease (prior stroke/TIA, coronary disease, or peripheral arterial disease) with greater cardiovascular risk and numerically larger absolute reductions in a broad cardiovascular event composite, but the treatment interaction did not meet conventional statistical significance (P=0.08) [31]. In a separate NOAH-AFNET 6 analysis, worsening estimated glomerular filtration rate correlated with more composite cardiovascular and safety events, largely reflecting cardiovascular death and other events rather than a clear increase in ischemic-stroke incidence; neither continuous eGFR nor CKD strata significantly modified randomized treatment effect (interaction P=0.50 and P=0.20, respectively) [32]. These analyses reuse parent-trial participants and do not add independent randomized sample sizes. Device modality is another source of risk heterogeneity, but not a randomized treatment-selection criterion. In a prespecified ARTESiA secondary analysis, 209 of 4,012 participants (5.2%) had subclinical AF documented by an implantable cardiac monitor (ICM), and 3,803 by a pacemaker or defibrillator. The ICM subgroup had more prior stroke/TIA (24.9% vs 7.7%). Among ICM recipients, stroke/systemic embolism occurred in 1/103 assigned apixaban and 9/106 assigned aspirin (0.3% vs 2.6% per year; HR 0.11, 95% CI 0.01–0.88); in pacemaker/defibrillator recipients, rates were 0.8% vs 1.2% per year (HR 0.69, 95% CI 0.49–0.98). The relative-scale treatment interaction was nonsignificant (P=.078), although the absolute risk-difference interaction was significant (P=0.002). Only ten stroke/systemic-embolism events occurred in the ICM stratum; nonrandom device indication, baseline risk imbalance and multiplicity caution against assuming monitoring technology independently predicts drug response [33]. Importantly, prognostic risk enrichment can increase the absolute number of events prevented even if the relative effect of anticoagulation is constant. That mathematical distinction provides a more defensible interpretation of these subgroup signals than claiming proven biological effect modification.

What Does Measured of Burden Predict—and What Does It Not?

In an ARTESiA secondary analysis with 3,986 participants with complete baseline rhythm data, 703 (17.6%) had no SCAF episode ≥6 minutes during the six months before randomization despite a previously documented qualifying episode. Of the remaining 3,283 with recent episodes, 2,542 had 1–5 episodes and 741 had ≥6. After

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adjustment for CHA_2DS_2-VASc and randomized treatment, ≥6 versus 1–5 episodes did not significantly predict stroke/systemic embolism (adjusted HR 0.89, 95% CI 0.59–1.34). The longest recent episode >6 hours compared with <1 hour was likewise not associated with increased stroke/systemic embolism (adjusted HR 1.02, 95% CI 0.63–1.66); the intermediate 1–6-hour group had adjusted HR 1.27 (95% CI 0.85–1.90) [34]. These baseline categories are not measures of cumulative percentage time in AF. Neither baseline episode frequency (treatment interaction P=.10) nor longest episode duration (treatment-effect trend P=0.10) significantly modified the relative benefit of apixaban [34]. Exploratorily, patients without a qualifying episode in the prior six months had lower subsequent stroke/systemic-embolism rates than those with recent episodes (0.5% vs 1.1% per patient-year; adjusted HR 0.48, 95% CI 0.27–0.85). This finding is not a validated reason to withhold anticoagulation. The January 2025 correction updated the formatting/counts for female sex in Table 1 and the baseline CHA_2DS_2-VASc value in Table 2 (>6-hour subgroup: 3.4 ± 1.2); it reported no alteration of clinical outcome estimates [35].

The negative interactions in ARTESiA do not establish that AF burden is universally unimportant. The sample was restricted to the enrolled range of subclinical episodes (<24 hours at baseline), and AF burden was represented by selected baseline episode counts and longest duration over a six-month window, not an updated cumulative AF-time exposure. Censoring at progression to clinical AF or longer SCAF, relatively low event rates, and restricted episode range further limit inference [34]. Moreover, in the ARTESiA progression analysis, the rate of stroke/systemic embolism after progression was 1.42% per patient-year among participants who continued blinded aspirin, versus 0.83% per patient-year among those receiving either blinded apixaban or open-label anticoagulation. Because treatment after progression was not randomly allocated, these descriptive comparisons are subject to treatment-selection bias and should not be used to calculate the causal benefit of a progression-triggered strategy [22]. A NOAH-AFNET 6 secondary analysis included only 259 participants with core-laboratory-verified AHRE ≥24 hours. Its broad efficacy composite occurred in 9/132 edoxaban-treated and 14/127 control participants;

Table 2: Clinical characteristics: prognosis versus anticoagulation response.

Characteristic / Analysis	Observed Signal	Strength and Limitation
CHA_2DS_2-VASc >4 (ARTESiA) [27]	3.95-point lower cumulative 3.5-y stroke/SE; 1.70-point more major bleeding (95% CI includes both directions)	n=1,085; relative interaction P=.23; absolute stroke-difference interaction P=.06; same ARTESiA cohort
CHA_2DS_2-VASc >4 (NOAH-AFNET 6) [28]	Efficacy composite 4.6 vs 5.3/100 patient-years (HR 0.88); death/major-bleeding composite 8.7 vs 5.6/100 patient-years (HR 1.59)	n=741; relative interactions P=.57 (efficacy) and P=.34 (safety); broad endpoints; exploratory, not an independent trial
Prior stroke/TIA (ARTESiA) [29]	7-point lower 3.5-y stroke/SE risk; ~3-point more bleeding	n=346; relative interaction P=.24; absolute interaction P=.03 tested post hoc (unadjusted)
Prior stroke/TIA (NOAH) [30]	4 vs 6 strokes; 8 vs 2 major bleeds	n=253; small-event, inconclusive secondary analysis
Vascular disease (pooled) [31]	Greater apparent absolute composite CV benefit	Interaction P=.08; broader outcome, overlapping cohorts
Kidney disease (NOAH) [32]	Higher CV and bleeding risk as kidney function worsens	No statistically significant eGFR/CKD interaction; most excess CV risk was not stroke
Frequency/duration (ARTESiA) [34,35]	No baseline frequency/duration treatment interactions; exploratory no-recent-AF group had lower stroke/SE	n=3,986; six-month baseline assessment; progression-censored; 2025 correction only to baseline tables
AHRE ≥24 h (NOAH) [36]	No significant duration-by-treatment interaction	n=259; two ischemic strokes in each arm; efficacy interaction P=.65
Economic models [39–41]	Modeled 0.024 and 0.016 QALYs in Winstén studies; 0.107 QALYs in high-risk Lamy model	Different population/horizon/drug prices; not separate trials or directly interchangeable estimates
SCAF progression (ARTESiA) [22]	31.2% progressed over mean 4.1 y; mortality HR 2.12; adjusted stroke/SE HR 1.03 (NS)	Time-varying observational association; post-progression antithrombotics not randomized; progression model C=0.59
ICM vs PM/ICD (ARTESiA) [33]	ICM: 0.3% vs 2.6%/y stroke/SE; absolute interaction P=.002; relative interaction P=.078	ICM n=209; 10 events; many more prior strokes; not evidence device type causes differential DOAC response

Note: Cumulative 3.5-year differences are not annualized rates; secondary analyses, including the risk-score comparisons, reuse parent-trial participants and are not independent trials. Comparisons after AF progression are nonrandomized; ICM subgroup is small with differing clinical indications. Relative and absolute-scale treatment interactions are distinct. SE, systemic embolism; TIA, transient ischemic attack; CV, cardiovascular; ICM, implantable cardiac monitor; PM/ICD, pacemaker/implantable cardioverter-defibrillator.

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there were only two ischemic strokes in each arm. Neither the primary efficacy interaction by AHRE duration (P=0.65) nor the safety interaction (P=0.98) was significant [36]. However, this subgroup is too small for a precise ischemic-stroke treatment-effect estimate. ECG-documented AF developed more frequently among those with AHRE ≥24 hours (17.0% per patient-year) than with shorter AHRE (8.2% per patient-year). These progression rates provide prognostic context but do not establish a duration-triggered anticoagulation rule. Taken together, observational associations between burden and stroke and the randomized-trial secondary analyses are neither equivalent nor necessarily contradictory. The missing evidence is a prospective test of whether changing treatment according to validated measures of burden improves patient-important outcomes beyond a strategy based on clinical stroke and bleeding risk.

Net Clinical Benefit, Economics, Guideline Translation, And Patient Preferences

Clinical net benefit cannot be estimated by subtracting the number of major bleeds from the number of ischemic strokes. The events differ in severity, reversibility, functional consequences, and mortality; even among major bleeds, gastrointestinal events differ clinically from intracranial or fatal hemorrhage. Trial analyses also differ in follow-up definitions and treatment changes after AF progression. A defensible comparison should specify baseline risks, time horizon, outcome weights, competing death, and uncertainty. Published trials did not validate a universal utility-weighted cutoff for anticoagulation [23-26]. Time-to-event modeling adds a clinically relevant but assumption-dependent dimension. Huang and colleagues reconstructed survival data from the published ARTESiA and NOAH-AFNET 6 curves (6,548 randomized participants) and estimated 2.67 years to prevent one additional stroke per 100 patients treated with a DOAC versus 1.67 years to cause one additional major bleed per 100. The corresponding pooled HRs were 0.67 for stroke (95% CI 0.50–0.90) and 1.57 for major bleeding (95% CI 1.21–2.04). These thresholds are model-derived, depend on baseline rates and the chosen 1% absolute-risk threshold, and do not weight stroke severity against bleeding severity. They reuse the same two trials and should not be interpreted as independently observed outcomes [37]. An alternative hierarchical assessment of the locked NOAH-AFNET 6 dataset (n=2,534) prioritized all-cause death, ischemic stroke, systemic/pulmonary embolism or myocardial infarction, and then major bleeding. The unmatched win ratio for edoxaban versus control was 0.87 (95% CI 0.68–1.10; P=.23), with 84.9% of patient pairs undecided; sensitivity hierarchies also failed to demonstrate a significant advantage. Although this post hoc approach integrates outcomes by rank, its findings are sensitive to the chosen hierarchy, use no new randomization, and cannot exclude smaller clinically meaningful effects [38].

Using a Markov model parameterized largely from ARTESiA and NOAH-AFNET 6, Winstén and colleagues estimated 0.024 additional quality-adjusted life-years (QALYs) per anticoagulated person over ten years, with a 65.8% probability of positive net benefit in sensitivity analyses accounting for uncertainty in treatment effects [39]. Their 2026 economic model—an extension with updated assumptions and Nordic health-system costs—estimated a 0.016-QALY gain, an additional €1,676 per person, and an incremental cost-effectiveness ratio of €105,293/QALY, versus a stated €50,000/QALY willingness-to-pay threshold [40]. The models are related analyses, not independent empirical confirmation, and their two QALY estimates should not be interpreted as a consistent, directly observed treatment effect. Assumptions concerning event severity, drug adherence, progression to clinical AF, and prices determine the results. Lamy and colleagues examined the ARTESiA subgroup with CHA_2DS_2-VASc >4, using actual trial events for in-trial costs and a modeled lifetime horizon for quality-adjusted outcomes [41]. Under study-specific, historical drug-price inputs, apixaban was estimated to be cost-saving in Canada and the United Kingdom; it yielded modeled lifetime incremental cost-effectiveness ratios of US$24,514/QALY in Germany and US$85,140/QALY in the United States, with a projected 0.107-QALY gain. On the authors' US base-case pricing and US$50,000/QALY threshold, treatment was not cost-effective. This does not contradict the Winstén models: populations (high-risk vs trial-average), comparators, horizons, utilities, medication prices, and health systems differ. It also does not demonstrate a new randomized relative treatment effect. In patients without previous ECG-documented AF, the 2023 ACC/AHA/ACCP/HRS guideline states that anticoagulation is reasonable for device-detected AHRE ≥24 hours with CHA_2DS_2-VASc ≥2 or equivalent stroke risk (Class IIa), and may be reasonable for episodes from 5 minutes to <24 hours with CHA_2DS_2-VASc ≥3 or equivalent risk (Class IIb), within shared decision-making. An AHRE <5 minutes without another indication should not trigger anticoagulation (Class III: No Benefit) [2]. The 2024 ESC guideline states that a direct oral anticoagulant may be considered in selected asymptomatic device-detected subclinical AF patients with high estimated thromboembolic risk and no major bleeding risk factors; the duration or burden justifying therapy remains uncertain [3]. These are clinical recommendations under uncertainty, not treatment cutoffs prospectively validated by ARTESiA or NOAH-AFNET 6. Clinical deliberation should confirm the rhythm source (and whether ECG-documented AF already exists); characterize episode recency, longest duration, and longitudinal measurements without treating them as interchangeable; estimate clinical stroke risk, prior stroke/TIA, vascular disease, kidney disease, and bleeding hazards; review antiplatelet indications and drug interactions; and present absolute outcome estimates tied to a specific

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source population and time horizon. Patient values and treatment burdens should be reconsidered as rhythm and comorbidities evolve. This remains a conceptual checklist, not a prospectively validated decision algorithm. Figure 1 illustrates these evidence domains without implying that the sequence has been prospectively validated.

Emerging Concepts, Evidence Gaps, and Future Research

Research priorities include harmonized classification of AHRE versus electrogram-confirmed SCAF; standardized reporting of monitoring interval, episode count, longest duration, and percentage time in AF; and external validation of calibrated, absolute stroke and bleeding predictions. An individual-participant-data synthesis of the two trials could seek consistent outcome definitions and analysis estimands, account for changes in treatment after AF progression, and distinguish baseline prognosis from relative treatment-effect modification. Any subgroup assessment requires prespecification, multiplicity-aware interpretation, and appropriate protection against deriving cutoffs from unstable small-event categories. Trials of longitudinal monitoring-guided treatment strategies are needed before burden-triggered initiation or withdrawal of anticoagulation is considered proven safe. Designs should prespecify clinically meaningful outcomes, including disabling ischemic stroke, symptomatic intracranial hemorrhage, other major bleeding, cardiovascular death, and patient-reported function, with transparent competing-risk handling. Causal treatment-strategy evaluations should anticipate time-varying confounding, adherence changes, treatment crossover, and progression to clinically documented AF. External validity also requires study in diverse populations, varying monitoring platforms, individuals with recent stroke, and patients with high bleeding susceptibility; neither implanted-device trial establishes treatment benefit after an isolated wearable photoplethysmography notification. The evidence base should expand beyond the predominant older, relatively high-risk populations and examine implementation feasibility, access, cost, and patient preferences. Several recent reviews address AF burden, anticoagulation, and individualized net clinical benefit: Wu and Hao discuss AF burden [42], Llerena-Velastegui and colleagues review trial interpretation [43], Scott presents a practical phenotype-led pathway [44], and Liu and colleagues focus on previous stroke/TIA [45]. The contribution of this article is not another duration-only treatment algorithm, but an explicit appraisal of prognostic versus predictive evidence, nonidentical trial estimands and censoring rules, overlapping secondary-analysis populations, and the sensitivity of benefit–harm assessments to patient characteristics, event severity, time horizon, and economic assumptions. These distinctions support an individualized approach while identifying priorities for prospective validation.

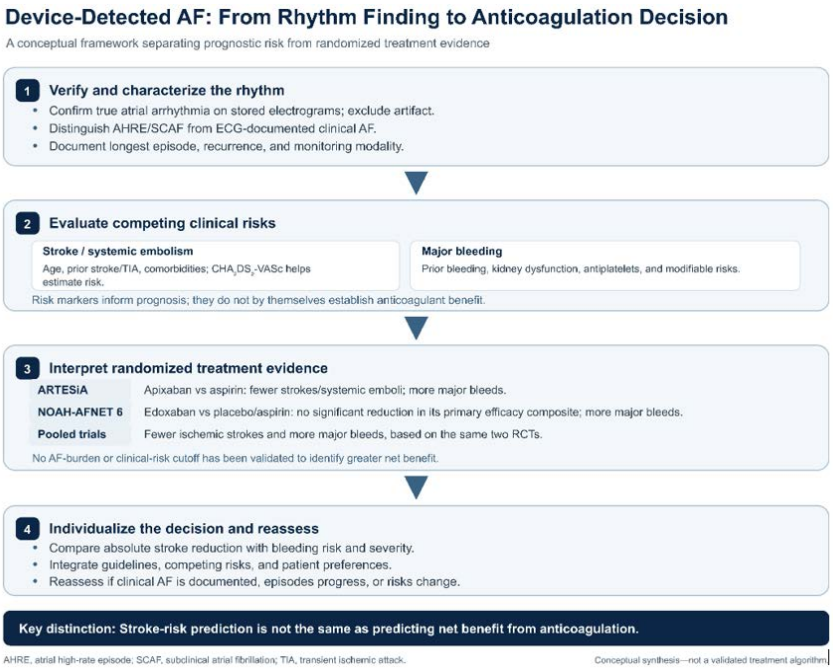


Figure 1: Clinical framework for anticoagulation decisions in device-detected atrial fibrillation.

Note: Figure legend: The conceptual framework distinguishes confirmation and characterization of device-detected AF, assessment of stroke and bleeding prognosis, and randomized evidence about anticoagulation effects. It emphasizes absolute benefits and harms, shared decision-making, and longitudinal reassessment; it is not a validated prediction rule or treatment algorithm. AHRE, atrial high-rate episode; SCAF, subclinical atrial fibrillation; TIA, transient ischemic attack.

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Conclusions

Among patients with elevated stroke risk and implanted-device–detected atrial arrhythmias, randomized and pooled evidence supports ischemic stroke reduction with the evaluated anticoagulants but also shows greater major bleeding. ARTESiA established a stroke/systemic embolism benefit for apixaban; NOAH-AFNET 6 did not establish a statistically significant benefit for edoxaban on its broader efficacy composite. Absolute clinical trade-offs vary, and neither baseline episode duration nor clinical risk subgroups have yielded universally validated treatment cutoffs. Distinguishing rhythm-confirmed diagnoses, baseline prognosis, relative treatment response, competing outcomes, and patient-specific values is more defensible than treating AF duration alone as a mandate for therapy.

Key Points

- Device-detected AHRE, electrogram-confirmed subclinical AF, ECG-diagnosed clinical AF, and wearable alerts should not be treated as interchangeable diagnoses.
- Longest episode, episode count, and cumulative proportion of time in AF measure different dimensions of arrhythmia exposure.
- Observational associations between AF burden and stroke risk do not establish an anticoagulation threshold.
- ARTESiA demonstrated fewer strokes or systemic embolic events with apixaban but more major bleeding; secondary analysis locates much of the excess in gastrointestinal bleeding, without demonstrating equivalence for intracranial or fatal events.
- NOAH-AFNET 6 did not demonstrate a significant benefit on its broader primary efficacy composite, while the death/major-bleeding safety composite increased; the study ended early.
- The study-level synthesis of these same two randomized trials found lower ischemic stroke risk and more major bleeding, without a demonstrated mortality benefit.
- Higher clinical stroke risk can increase absolute event risk, but ARTESiA and NOAH-AFNET 6 subgroup analyses have not established a reproducible CHA_2DS_2-VASc threshold that predicts greater relative treatment benefit.
- ARTESiA baseline episode frequency and longest episode duration did not significantly modify apixaban benefit in a secondary analysis restricted to the studied episode range.
- Future research should test prospectively validated, dynamic, preference-sensitive decision strategies using harmonized clinical outcomes.

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Ethics Approval Declaration and Data Availability

No new pre-clinical or clinical studies were performed, and all findings were gathered from the published articles and critically reviewed. Hence, an approval from the Institutional Review Board or any other Approval Committee for Ethics Approval is not applicable. All collected findings and their analyses are available with the corresponding author upon request through the proper channel.

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Competing Interests

All authors have read the manuscript and declare no conflict of interest. No writing assistance was utilized in the production of this manuscript.

Consent for Publication

All authors have read the manuscript and consented for publication.

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