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Anticoagulation versus Antiplatelet Therapy After Cancer-Associated Ischemic Stroke: A Net-Benefit Threshold Analysis

Hyun Dong Yoo
Eulji University Hospital
Jae Guk Kim
Eulji University Hospital
Seung Young Chung
neurocsy@gmail.com

Eulji University Hospital

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Abstract

Background

Cancer-associated ischemic stroke carries high risks of recurrent thromboembolism and death, but the optimal antithrombotic strategy for secondary prevention remains uncertain. Comparative evidence informs treatment ranking but does not define the recurrence–bleeding trade-off at which anticoagulation becomes net-beneficial.

Methods

We developed a short-horizon, mortality-adjusted net-benefit threshold model comparing anticoagulation with antiplatelet therapy over a 6-month horizon (utility-weighted clinical net benefit; costs excluded). The anticoagulation effect on recurrence was treated as a threshold variable, not a fixed effect. Randomized head-to-head recurrence estimates in cancer-relevant populations were extracted to derive evidence-informed priors; probabilistic sensitivity analysis (10,000 simulations) was run under a legacy broad comparison prior and two evidence-informed priors, positioning available estimates against the break-even.

Results

At the base-case 2% excess major-bleeding level, anticoagulation became net-beneficial only below a recurrence relative risk of 0.825 (break-even). The probability that anticoagulation was favored was 0.44 under the legacy broad comparison prior but fell to 0.12 (ARCADIA-informed neutral) and 0.04 (NAVIGATE-cancer-informed skeptical) under the evidence-informed priors. Available randomized head-to-head estimates were wide and indirect and lay predominantly at or above the break-even (NAVIGATE-ESUS cancer hazard ratio 1.43 [0.71–2.87]; main ARCADIA 1.00 [0.64–1.55]), with only an underpowered cancer-history crude estimate (≈ 0.69) below it; the two formal intervals crossed both the break-even and the null.

Conclusions

Current randomized evidence does not demonstrate a recurrence reduction sufficient to make anticoagulation net-beneficial under base-case harm assumptions. The remaining uncertainty reflects imprecise, indirect evidence rather than a demonstrated anticoagulation advantage, supporting a future confirmatory trial rather than a change in practice.

Background

Cancer-associated ischemic stroke carries a high risk of recurrent thromboembolism and death, and its mechanisms are heterogeneous: roughly half of strokes in patients with active cancer follow conventional mechanisms, while the remainder are cryptogenic or attributable to cancer-specific, hypercoagulable processes characterized by features such as markedly elevated D-dimer, multiple-territory infarction, and metastatic disease [1, 2, 3].

For secondary prevention in this setting, the choice between anticoagulation and antiplatelet therapy remains unresolved. Contemporary syntheses and a recent scientific statement describe genuine uncertainty about the optimal antithrombotic strategy and call for dedicated trials [1, 2].

Existing evidence is informative but does not answer the bedside question directly. A cancer-specific network meta-analysis provides endpoint-specific treatment rankings [4], and randomized or randomized-derived data remain small or indirect [5, 6, 7]. None of these resolves the threshold question that drives the individual decision: how large a reduction in recurrence would be required, at what cost in excess bleeding, and within what expected survival, for anticoagulation to be net-beneficial.

We therefore developed a short-horizon, mortality-adjusted net-benefit threshold model that integrates recurrence prevention, hemorrhagic harm, and competing mortality, treating the anticoagulation effect as a threshold variable rather than a fixed estimate. Its aim is to characterize the conditions under which anticoagulation would be net-beneficial and to quantify the residual decision uncertainty relevant to future trial design.

Methods

Study design and reporting framework

This was an original decision-analytic modeling study based on published, aggregate-level evidence. It is **not** a treatment-ranking meta-analysis and does not attempt to estimate a pooled comparative treatment effect. Instead, we construct a short-horizon, mortality-adjusted net-clinical-benefit **threshold model** to identify the conditions under which anticoagulation provides greater net clinical benefit than antiplatelet therapy for secondary prevention after cancer-associated ischemic stroke. The analysis asks *when* one strategy becomes preferred, rather than *which* strategy ranks higher on any single endpoint. The model was developed and is reported in accordance with the ISPOR–SMDM Modeling Good Research Practices recommendations, drawing on the task-force reports covering overall modeling conduct [8], state-transition modeling [9], and parameter estimation and uncertainty analysis [10]. Costs are excluded by design; the analysis is restricted to clinical net benefit expressed in quality-adjusted (utility-weighted) terms, which distinguishes it from prior cost-effectiveness analyses in adjacent populations.

Target population and comparators

The target population is adults with active cancer and ischemic stroke in whom cancer-associated hypercoagulability is a plausible stroke mechanism — the high-risk subgroup characterized by features such as multiple-territory infarction, markedly elevated D-dimer, and metastatic disease [1, 2]. Two secondary-prevention strategies are compared as broad classes: (i) antiplatelet therapy (AP) and (ii) anticoagulation (AC). The base case treats anticoagulation as a broad class; agent-specific differences between low-molecular-weight heparin and direct oral anticoagulants are addressed qualitatively in the interpretation and limitations because available head-to-head recurrence and bleeding data are sparse. Withholding antithrombotic therapy is not a base-case comparator and is considered only as a terminal/very-high-bleeding-risk scenario. Cardioembolic stroke attributable to atrial fibrillation is handled separately and is not the base-case population.

Model structure

A short-horizon decision tree is used for the base case, reflecting the substantial competing mortality that active cancer introduces over a limited horizon. From each strategy, modeled health outcomes are: (a) no recurrent event; (b) recurrent ischemic stroke or systemic embolic event; (c) major bleeding, including intracranial hemorrhage (ICH); (d) cancer-related or other non-stroke death; and (e) death following a recurrent thrombotic or bleeding event. Outcomes are weighted by health utility to yield quality-adjusted survival over the horizon, and the primary model quantity is the incremental net benefit (INB) of anticoagulation versus antiplatelet therapy (INB = QALY_AC − QALY_AP). A longer-horizon Markov extension is not used in the base case. A schematic of the model structure is provided in Supplementary Figure S1.

Time horizon

The base-case horizon is 6 months from the index ischemic stroke, chosen because active-cancer competing mortality limits the window over which secondary prevention can accrue benefit. The horizon is treated as a structural modeling assumption rather than as a source-derived estimate.

Evidence-source hierarchy

Inputs are assigned according to a pre-specified hierarchy that separates *effect* parameters from *baseline-risk* and *scenario* parameters (full mapping in Table 1 and Supplementary Table S1).

Table 1

Model input parameters (base case and probabilistic distributions). Values are model inputs; where evidence is sparse they are not established point estimates. Status indicates how each parameter is treated.

Sources are listed in the numbered reference list.

Domain	Parameter	Base-case value / distribution	Status	Primary source / rationale
Structure	Time horizon	0.5 year (structural modeling assumption)	Fixed (structural)	Short horizon chosen because active-cancer competing mortality limits the benefit window.
Recurrence	Baseline recurrence under AP	0.08 over 6 months	Base-case assumption	Plausibility-anchored to cancer-stroke literature (NMA source data [4] and cohorts); not an extracted point estimate; varied via RR and horizon.
Recurrence	AC recurrence relative risk (RR)	deterministic verification value 1.00; PSA priors — legacy broad **Uniform(0.40–1.10)** (comparison only) and two evidence-informed lognormal priors: ARCADIA-informed neutral (HR 1.00, 95% CI 0.64–1.55) and NAVIGATE-cancer-informed skeptical (HR 1.43, 95% CI 0.71–2.87)	**Threshold variable**	NOT a fixed effect. Evidence-informed priors derived from extracted randomized head-to-head estimates (NAVIGATE-ESUS cancer subgroup [6]; main ARCADIA trial [11]); hazard ratios used as relative-effect priors on the log scale (indirectness). Pipek et al. [4] = ranking/directional anchor only.
Bleeding	Excess major bleeding with AC	base 0.02; PSA **Triangular(0.00, 0.02, 0.08)**	Scenario range; not a fixed point estimate	Wide range: lower bound = no clear between-strategy difference [4, 7]; upper tail = observational signals of increased bleeding with AC. Arm-level counts sparse.
Bleeding	ICH fraction among major bleeds	0.30; scenario (low / intermediate / high)	Scenario range; not a fixed point estimate	Scenario parameter; arm-level ICH counts sparse; high-ICH scenario informed by anticoagulant type / brain involvement.
Bleeding	Weighted bleeding harm, *W*	0.14	Derived	*W* = (1 − ICH fraction) × d_bleed + ICH fraction × d_ICH = 0.7×0.05 + 0.3×0.35.
Competing mortality	6-month competing mortality	base 0.30; PSA **Triangular(0.20, 0.30, 0.45)**	Interpolated scenario parameter	Anchored to Taipei VGH cohort (Lee et al. [12]; CAS n = 39; 30-day mortality 17.9%, 1-year mortality 51.3% confirmed); **6-month value**

Domain	Parameter	Base-case value / distribution	Status	Primary source / rationale
				interpolated between the confirmed 30-day and 1-year mortality, not directly observed. Validation/range: SCAN [13], ASTRAL/Costamagna [14]. High-mortality scenario: Navi [3], Oka [15]. Non-differential between strategies in base case.
Utility	mRS utility anchors (EQ-5D-3L)	mRS 0/1/2/3/4/5 = **0.90 / 0.82 / 0.70 / 0.54 / 0.24 / −0.14**; death = 0 (by model definition)	Locked anchor	Ali et al. [16] (PMC6027777), UK EQ-5D-3L value set, mRS-stratified observed mean utilities (Supplement III). Endpoint values (mRS 0 = 0.90, mRS 5 = − 0.14) are consistent with the abstract-reported ranges; the UK column is taken from Supplement III.
Utility	Recurrent stroke disutility	base 0.20; PSA **Triangular(0.10, 0.20, 0.35)**	Pragmatic scenario input	Pragmatic scenario input informed by the mRS utility anchors reported by Ali et al. [16]; varied over a wide prespecified PSA range. Rivero-Arias [17] = mRS→EQ-5D mapping methodology only.
Utility	Major bleeding disutility	base 0.05; PSA **Triangular(0.02, 0.05, 0.10)**	Pragmatic scenario input	Pragmatic scenario input informed by the mRS utility anchors reported by Ali et al. [16]; varied over a wide range. Rivero-Arias [17] = methodology only.
Utility	ICH disutility	base 0.35; PSA **Triangular(0.20, 0.35, 0.55)**	Pragmatic scenario input	Pragmatic scenario input informed by the mRS utility anchors reported by Ali et al. [16]; varied over a wide range. Rivero-Arias [17] = methodology only.

- **Comparative treatment effect (recurrence).** No fixed comparative effect is assumed; the anticoagulation-versus-antiplatelet recurrence effect is modeled as a threshold variable (see below). To position this variable against data, a targeted extraction of randomized head-to-head estimates of recurrent stroke under anticoagulation versus antiplatelet therapy in cancer-relevant populations was performed (Supplementary Table S2). Two estimates were judged usable to inform probabilistic priors: the NAVIGATE-ESUS cancer subgroup (rivaroxaban vs aspirin; hazard ratio [HR] 1.43, 95% confidence interval [CI] 0.71–2.87) [6] and the main ARCADIA trial (apixaban vs aspirin; HR 1.00,

95% CI 0.64–1.55) [11], both indirect to active-cancer hypercoagulable stroke (see Limitations). The cancer-specific network meta-analysis of Pipek et al. [4] reports treatment rankings and contrasts versus no treatment rather than an extractable anticoagulation-versus-antiplatelet pairwise estimate, and is therefore used as a ranking/directional anchor only. The small ARCADIA cancer-history subgroup (apixaban vs aspirin; crude recurrent-stroke rate 8.2% vs 11.8%) [7] provided no formal hazard ratio and was underpowered, and the TEACH pilot [5] was a feasibility trial not powered for clinical endpoints; neither was used to form a prior.

- **Baseline risks.** Baseline recurrence and bleeding risks were anchored to the cancer-stroke antithrombotic literature, including network-meta-analytic source data and observational cohorts, but were not treated as definitive point estimates when arm-level event counts were sparse. Strategy-stratified comparisons from observational data are regarded as confounded by indication and are therefore used to inform scenario/range inputs, never as treatment-effect estimates.
- **Competing mortality.** Six-month competing mortality is anchored primarily to the Taipei Veterans General Hospital cohort [12], which reports 30-day mortality (17.9%) and 1-year mortality (51.3%) in the cancer-associated-stroke subgroup (n = 39). The 6-month value was not directly reported and was therefore treated as an **interpolated scenario parameter — between the confirmed 30-day and 1-year mortality — rather than an observed cohort estimate.** Additional active-cancer-stroke cohorts are used as validation/range anchors, including the SCAN parent survival study [13] and the ASTRAL registry analysis [14], and as high-mortality scenario anchors [3, 15].
- **Sensitivity bounds only.** Evidence from cancer-associated venous thromboembolism and from brain-tumor populations is used solely to bound bleeding/ICH sensitivity ranges and never as primary evidence for stroke recurrence or for the base-case bleeding rate.

Parameterization

The anticoagulation-versus-antiplatelet effect on recurrence is treated as a **threshold variable** rather than a fixed estimate. For probabilistic analysis it is assigned three pre-specified priors on the relative-risk scale. The **legacy broad** prior, Uniform(0.40, 1.10), was retained only for comparison with the initial analysis; because it places substantial probability mass below the break-even threshold, it should not be interpreted as evidence-informed or direction-neutral. Two **evidence-informed lognormal priors** are derived from the extracted randomized head-to-head estimates (see above): an **ARCADIA-informed neutral** prior centred on HR 1.00 (95% CI 0.64–1.55) and a **NAVIGATE-cancer-informed skeptical** prior centred on HR 1.43 (95% CI 0.71–2.87). Each lognormal prior uses $\mu = \ln(\text{point estimate})$ and $\sigma = [\ln(\text{upper}) - \ln(\text{lower})] / (2 \times 1.96)$; no upper bound is imposed, so net harm from anticoagulation is retained as a possibility. Because the extracted estimates were reported as hazard ratios, they were used as recurrence relative-effect priors on the log scale; this approximation is treated as part of the indirectness of the evidence (see Limitations) rather than as a direct pooled relative-risk estimate. The unstable indirect ratio derivable from the Pipek versus-no-treatment estimates ($0.50/0.44 \approx 1.14$) was not used as a prior because no covariance or pairwise interval is available, and the ARCADIA cancer-history crude estimate (≈ 0.69) was not used because it lacks a formal interval (see above).

Because arm-level major-bleeding and ICH event counts are sparse in active-cancer ischemic stroke, bleeding risk and ICH fraction are handled as wide threshold/scenario ranges rather than as fixed point estimates. The excess major-bleeding risk associated with anticoagulation is represented by a wide triangular range (Triangular(0.00, 0.02, 0.08)); the lower bound reflects syntheses showing no clear between-strategy difference, and the positive tail reflects observational signals of increased bleeding with anticoagulation. ICH fraction among major bleeds is treated as a scenario parameter (low/intermediate/high), with an additional high-ICH scenario. None of these bleeding/ICH values is an established figure; they are treated as wide scenario ranges rather than source-locked point estimates. Competing-mortality parameters use the anchors described above, with a base-case 6-month mortality distribution (Triangular(0.20, 0.30, 0.45)) and a separate high-mortality scenario. All base-case values and probabilistic distributions are listed in Table 1, with detailed sourcing, use, status, and caveats in Supplementary Table S1.

Utility and net clinical benefit

Net clinical benefit is expressed in utility-weighted (quality-adjusted) terms; costs are not included. Health states are weighted by mRS-based utilities. The mRS health-state utility anchors are the UK EQ-5D-3L value-set observed means reported by Ali et al. [16] (mRS 0/1/2/3/4/5 = 0.90/0.82/0.70/0.54/0.24/−0.14; death = 0 by model definition), and the mRS→EQ-5D mapping methodology is that of Rivero-Arias et al. [17], cited as a **methodology citation only.** The event-disutility values (recurrent ischemic stroke, major bleeding, and ICH; Table 1, Supplementary Table S1) are **pragmatic scenario inputs informed by these mRS utility anchors and varied over wide prespecified PSA ranges**, rather than values directly extracted from any single source. A pre-specified sensitivity analysis varies the relative weighting of ischemic versus hemorrhagic events (including an unweighted comparison), because the relative valuation of these events is contested.

Deterministic sensitivity analysis

The principal deterministic analysis evaluates the strategy-preference boundary across the anticoagulation recurrence relative risk and the excess major-bleeding risk, with competing mortality incorporated as a non-differential horizon-level attenuation factor. It is presented as a two-way **threshold surface** on which the contour of zero incremental net benefit separates the regions favouring each strategy (Fig. 1); a numerical companion across bleeding-harm assumptions is provided in Supplementary Table S3. Because competing mortality is non-differential between strategies in the base case, it attenuates the absolute magnitude of net benefit but does not independently move the preference boundary. Strategy-specific fatality or differential-mortality assumptions are not modeled as primary inputs and are considered only as exploratory extensions.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis is performed by Monte Carlo simulation over all uncertain inputs using the distributions defined above and in Table 1, with a seeded random-number generator for reproducibility (seed 20260613). Outputs include the probability that anticoagulation is favored, the distribution and **simulation interval (2.5th–97.5th percentile)** of incremental net benefit, and per-iteration parameter draws retained for transparency. The recurrence relative risk is represented by the three priors defined above — a legacy broad comparison prior and two evidence-informed lognormal priors (ARCADIA-informed neutral; NAVIGATE-cancer-informed skeptical) — each propagated through the same seeded simulation so that only the recurrence prior differs across analyses.

Value-of-information analysis

To express residual decision uncertainty, the expected value of perfect information (EVPI) is computed at the per-patient level as mean(max(QALY_AC, QALY_AP)) − max(mean(QALY_AC), mean(QALY_AP)). EVPI is reported as a **secondary** output that contextualizes the value of a future confirmatory randomized trial rather than as a primary result. The expected value of partial perfect information (EVPPI) was not performed at this stage, as it would exceed the scope of this preliminary short-horizon model. Because the evidence-informed priors place most probability mass beyond the break-even relative risk, the resulting per-patient EVPI is small; accordingly, the rationale for a future trial is framed primarily in terms of the indirectness and imprecision of the available estimates rather than the magnitude of EVPI.

Targeted evidence extraction

A targeted extraction of randomized head-to-head estimates of recurrent stroke under anticoagulation versus antiplatelet therapy in cancer-relevant populations was performed to anchor the evidence-informed recurrence priors (see above) and the break-even comparison (see Results; Supplementary Table S2). Extraction recorded population (active cancer versus cancer history), comparator, follow-up, the recurrence estimate with its interval where available, and bleeding and mortality where reported, and classified each source as usable for a prior, ranking/directional only, or not usable; values that could not be extracted were recorded as such rather than imputed. Baseline-risk, bleeding/ICH, and competing-mortality parameters remain scenario/range inputs anchored to existing syntheses and cohorts (see above); study-level event-count extraction to fix these parameters was not performed, as it would imply a precision the underlying evidence does not support.

Scope exclusions

This study does not (a) conduct a treatment-ranking or pooled-effect meta-analysis; (b) perform a cost-effectiveness or cost-utility analysis; (c) generate new pooled biomarker-subgroup effect estimates; or (d) extrapolate beyond the modeled horizon. The contribution is a short-horizon, mortality-adjusted net-benefit threshold framework that integrates recurrence prevention, hemorrhagic harm, and limited survival into a single decision-relevant model.

Use of large language models

A large language model (Claude; Anthropic, San Francisco, CA, USA) was used to assist with language editing and stylistic refinement of the manuscript. The study concept, the decision-analytic model and all of its parameter inputs, the analyses, and the interpretation of the results are the work of the authors, who reviewed and verified all content and take full responsibility for it. The large language model does not meet authorship criteria and is not listed as an author.

Results

Model feasibility and parameterization

The model executed end-to-end over the 6-month base-case horizon for both strategies, producing utility-weighted survival and incremental net benefit (INB) without structural error. The frozen base-case input vector and probabilistic distributions are given in Table 1 (detailed sourcing and caveats in Supplementary Table S1), with each input labeled by status: threshold variable (recurrence relative risk, RR), scenario/range (excess major bleeding, ICH fraction), interpolated scenario parameter [12], and methodology-defined [16, 17]. The weighted bleeding-harm term used in the base case was W = (1 − ICH fraction)·d_bleed + ICH fraction·d_ICH = 0.14.

Base-case calculation

Reported as a model-verification step. At the base-case parameter set (RR = 1.00; 2% excess bleeding; 6-month mortality 0.30; W = 0.14), incremental net benefit was **− 0.00098 QALY** — marginally negative — confirming correct model behavior (INB rises as RR falls and falls as excess bleeding rises).

Deterministic threshold analysis

The principal deterministic output is the two-way threshold surface over the recurrence RR and the excess major-bleeding risk, with the contour at which INB = 0 defining the strategy-preference boundary (Fig. 1). At the base-case excess-bleeding level (2%), anticoagulation became net-beneficial below a break-even recurrence relative risk of **0.825**; the boundary shifts toward more stringent (lower) RR as excess bleeding increases and reaches the lower modeled RR bound (0.40) near ~ 6.9% excess bleeding. Because competing mortality is non-differential between strategies in the base case, it changes the magnitude of INB but does not by itself move the preference boundary. A deterministic grid of the break-even relative risk across bleeding-harm assumptions accompanies Fig. 1 (Supplementary Table S3).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was repeated under each of the three recurrence-effect priors (see Methods; Fig. 2). Under the legacy broad comparison prior (recurrence relative risk ~ Uniform[0.40, 1.10]), the probability that anticoagulation was favored was **0.44** (median relative risk 0.75), with incremental net benefit (INB) mean **− 0.00023 QALY** and a 2.5th–97.5th-percentile simulation interval of **(− 0.0033, + 0.0029)** straddling zero. Under the two evidence-informed lognormal priors this probability fell substantially: **0.12** under the ARCADIA-informed neutral prior (median relative risk 1.00; INB mean −

0.00187 QALY; 2.5th–97.5th-percentile interval (− 0.0057, + 0.0010)) and **0.04** under the NAVIGATE-cancer-informed skeptical prior (median relative risk 1.44; INB mean − 0.00485 QALY; interval (− 0.0138, + 0.0004)) (Fig. 2). Across the evidence-informed priors the INB distribution shifted away from zero toward antiplatelet-favored values, indicating that when the recurrence prior was anchored to randomized head-to-head estimates rather than to the legacy broad comparison range, anticoagulation was favored in only a small minority of simulations. Per-iteration draws are retained for reproducibility (seed 20260613).

Position of available evidence relative to the break-even

To make the threshold interpretable against data, the available randomized head-to-head recurrence estimates were positioned relative to the base-case break-even relative risk (0.825; Fig. 3). Both formally estimable contrasts lay at or above the break-even: the NAVIGATE-ESUS cancer subgroup (rivaroxaban vs aspirin; HR 1.43, 95% CI 0.71–2.87) [6] and the main ARCADIA trial (apixaban vs aspirin; HR 1.00, 95% CI 0.64–1.55) [11]. The only estimate below the break-even was the small ARCADIA cancer-history subgroup crude rate (apixaban vs aspirin, ≈ 0.69) [7], which lacked a formal interval and was underpowered. Each estimable interval crossed both the break-even and the null (relative risk 1.00), and the Pipek network meta-analysis [4] provided only a treatment ranking (antiplatelet highest for recurrence in the primary analysis; low-molecular-weight heparin higher than antiplatelet in subgroups) without an extractable pairwise estimate. Available randomized evidence therefore lay predominantly at or above the break-even relative risk required for anticoagulation to be net-beneficial under base-case bleeding assumptions, with intervals too wide to exclude either net benefit or net harm.

Evidence-gap assessment

Residual decision uncertainty was summarized by the per-patient EVPI, which was small and decreased as the recurrence prior became evidence-informed (legacy 0.00054; ARCADIA-informed neutral 0.00008; NAVIGATE-cancer-informed skeptical 0.00003 QALY), reflecting that the evidence-informed priors place most probability mass beyond the break-even; EVPI is reported only as a secondary descriptor (EVPPI not performed). Bleeding and ICH inputs remained wide scenario ranges rather than source-locked point estimates, the 6-month competing-mortality anchor remained an interpolated scenario parameter, and the mRS utility anchors remained those of Ali et al. [16] with event disutilities treated as pragmatic scenario inputs. The available bleeding evidence was directionally inconsistent across anticoagulants — higher major bleeding with rivaroxaban in NAVIGATE-ESUS [6] but lower major hemorrhage with apixaban in the ARCADIA cancer subgroup [7] — supporting the decision to retain excess bleeding as a scenario range rather than a fixed value.

Summary. In this short-horizon threshold model, anticoagulation was not shown to be net-beneficial under current evidence. Anticoagulation would have to reduce recurrent ischemic stroke to a relative risk below 0.825 (under base-case bleeding assumptions) to become net-beneficial, whereas the available randomized head-to-head estimates were imprecise and lay predominantly at or above this break-even

threshold. The probability that anticoagulation was favored fell from 0.44 under the legacy broad comparison prior to 0.12 and 0.04 under evidence-informed priors. Current randomized evidence therefore does not demonstrate a recurrence reduction sufficient to make anticoagulation net-beneficial; the remaining uncertainty reflects imprecise and indirect evidence — supporting a future trial — rather than a demonstrated anticoagulation advantage.

Discussion

Principal findings

Using a short-horizon, mortality-adjusted net-benefit threshold model, anticoagulation was not shown to be net-beneficial under current evidence. The deterministic surface located a recurrence relative-risk boundary (break-even relative risk 0.825 at the base-case 2% excess bleeding; Fig. 1), and the probabilistic analysis showed that the probability of anticoagulation being favored fell from 0.44 under the legacy broad comparison prior to 0.12 and 0.04 once the recurrence prior was anchored to randomized head-to-head estimates (Fig. 2). Positioned against this break-even, the available randomized estimates lay predominantly at or above it — the NAVIGATE-ESUS cancer subgroup and the main ARCADIA trial at or above, with only an underpowered cancer-history crude estimate below — and the formal intervals crossed both the break-even and the null (Fig. 3). Current randomized evidence therefore does not demonstrate a recurrence reduction sufficient to make anticoagulation net-beneficial under base-case harm assumptions; these outputs should be read as a structured description of decision uncertainty, not as a treatment-effect estimate.

Clinical interpretation

In cancer-associated ischemic stroke, features such as markedly elevated D-dimer, multiple-territory infarction, and metastatic disease raise suspicion of a cancer-specific hypercoagulable mechanism and prompt consideration of anticoagulation [1, 2]. However, short expected survival and a competing risk of hemorrhage mean that a single average treatment effect is insufficient to settle the bedside decision. The value of a threshold framing is that it maps the decision onto quantities a clinician can reason about for an individual patient — how large a recurrence reduction is plausible, how much additional bleeding is expected, and what survival is anticipated — rather than collapsing these into one pooled comparison. The analysis does not recommend a strategy; it describes the conditions under which each strategy would be preferred.

Relation to prior evidence

Existing cancer-specific evidence is informative but does not answer the threshold question directly. The cancer-specific network meta-analysis of Pipek et al. [4] provides a treatment ranking across separate endpoints — antiplatelet ranked highest for recurrence, with no extractable anticoagulation-versus-antiplatelet pairwise estimate — and is used here only as a ranking/directional anchor. Randomized head-to-head data remain limited and indirect: a pilot feasibility trial [5], an embolic-stroke-of-

undetermined-source cancer subgroup [6], the main ARCADIA trial in cryptogenic stroke with atrial cardiopathy [11], and a small post hoc cancer-history subgroup [7] — each individually underpowered or indirect for the active-cancer decision. Rather than adding another ranking, this study positions these estimates against an explicit break-even and integrates recurrence prevention, hemorrhagic harm, and limited survival into a single decision-relevant threshold, operationalizing the therapeutic uncertainty already described in narrative and statement form [1, 2].

Implications for trial design

The analysis makes the design target explicit: a future trial would need to detect whether anticoagulation reduces recurrence to below the break-even relative risk (0.825 at the base-case bleeding level, corresponding to an approximately 17.5% relative recurrence reduction versus antiplatelet therapy), with the bleeding axis indicating how much additional major bleeding would reverse the preference. The rationale for such a trial rests on the indirectness of the available estimates (mostly cancer-history or non-cancer populations) and their imprecision, with formal intervals crossing both the break-even and the null, rather than on the expected value of perfect information, which was small under the evidence-informed priors and is reported only as a secondary descriptor (EVPPI was not performed). These outputs are trial-design–informing rather than practice-changing.

Limitations

Several limitations bound the interpretation and are reflected in the parameter status flags. First, arm-level major-bleeding and ICH event counts are sparse; bleeding and ICH fraction are handled as wide scenario ranges rather than source-locked point estimates, and specific bleeding figures — including the ARCADIA cancer post hoc values — are not locked. The available bleeding signal is itself directionally inconsistent across anticoagulants [6, 7], reinforcing the use of a scenario range. Second, 6-month competing mortality is not a directly observed value; it is an interpolated scenario parameter anchored to a single cohort [12], with validation/range and high-mortality behavior drawn from heterogeneous cohorts [3, 13, 14, 15]. Because competing mortality was assumed non-differential between strategies in the base case, it changes the magnitude of net benefit but does not by itself move the preference boundary; the base-case model is therefore mortality-adjusted rather than a strategy-specific competing-risk state-transition process, and differential-mortality assumptions should be interpreted only through separate exploratory scenario analyses. Third, the mRS health-state utility anchors are the UK EQ-5D-3L observed means reported by Ali et al. [16], while event disutilities were pragmatic scenario inputs varied over wide ranges; Rivero-Arias et al. [17] is cited as the mRS→EQ-5D mapping methodology only. Fourth, the evidence-informed priors were derived from hazard ratios used as recurrence relative-risk priors on the log scale; this approximation, together with the predominance of cancer-history and non-cancer populations among the source estimates, means the model is indirect to the active-cancer hypercoagulable hypothesis it is intended to inform. Fifth, and most fundamentally, the analysis does not estimate a treatment effect; the anticoagulation effect is treated as a threshold variable, so the model cannot and does not state which strategy is superior. Finally, the base case uses a short-horizon decision structure with broad comparator classes; longer horizons and low-molecular-weight-heparin

versus direct-oral-anticoagulant distinctions are discussed qualitatively rather than modeled. Accordingly, the model is hypothesis-generating and decision-structuring, not a guideline.

Conclusions

This model does not establish anticoagulation as superior or inferior. Under base-case harm assumptions, anticoagulation would need to reduce recurrent ischemic stroke to below a relative risk of 0.825 to be net-beneficial, whereas the available randomized head-to-head estimates were imprecise, indirect, and lay predominantly at or above this break-even; current randomized evidence therefore does not demonstrate, within its indirect and imprecise limits, a recurrence reduction sufficient to make anticoagulation net-beneficial. The remaining uncertainty reflects the limitations of existing evidence rather than a demonstrated anticoagulation advantage, supporting a future confirmatory trial rather than a change in practice.

Abbreviations

AC
anticoagulation
AHA
American Heart Association
AP
antiplatelet therapy
ARCADIA
Atrial Cardiopathy and Antithrombotic Drugs in Prevention After Cryptogenic Stroke
CI
confidence interval
DOAC
direct oral anticoagulant
EQ-5D-3L
EuroQol 5-Dimension 3-Level
ESUS
embolic stroke of undetermined source
EVPI
expected value of perfect information
EVPPI
expected value of partial perfect information
HR
hazard ratio
ICH
intracranial hemorrhage
INB

incremental net benefit
ISPOR-SMDM
International Society for Pharmacoeconomics and Outcomes Research–Society for Medical Decision Making
LMWH
low-molecular-weight heparin
mRS
modified Rankin Scale
NMA
network meta-analysis
PSA
probabilistic sensitivity analysis
QALY
quality-adjusted life year
RR
relative risk
TEACH
Trial of Enoxaparin versus Aspirin in Patients with Cancer and Stroke
VTE
venous thromboembolism.

Declarations

Ethics approval and consent to participate

Not applicable. This decision-analytic modeling study used only previously published, aggregate-level data and did not involve human participants, individual patient data, human tissue, or animals; institutional review board approval and informed consent were therefore not required.

Consent for publication

Not applicable.

Availability of data and materials

All data analyzed in this study were derived from previously published sources, which are cited in the manuscript. The reproducible model code, parameter inputs, and probabilistic-analysis scripts generated during the current study are available in the Open Science Framework (OSF) repository (https://osf.io/35em6 and https://osf.io/t29s4) and are also provided as Additional files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HDY conceived and designed the decision-analytic model, performed the analysis, and drafted the manuscript. JGK contributed to the clinical framing, identification and appraisal of the evidence, and interpretation, and critically revised the manuscript for important intellectual content. SYC supervised the study, contributed to model conceptualization and interpretation, and critically revised the manuscript. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

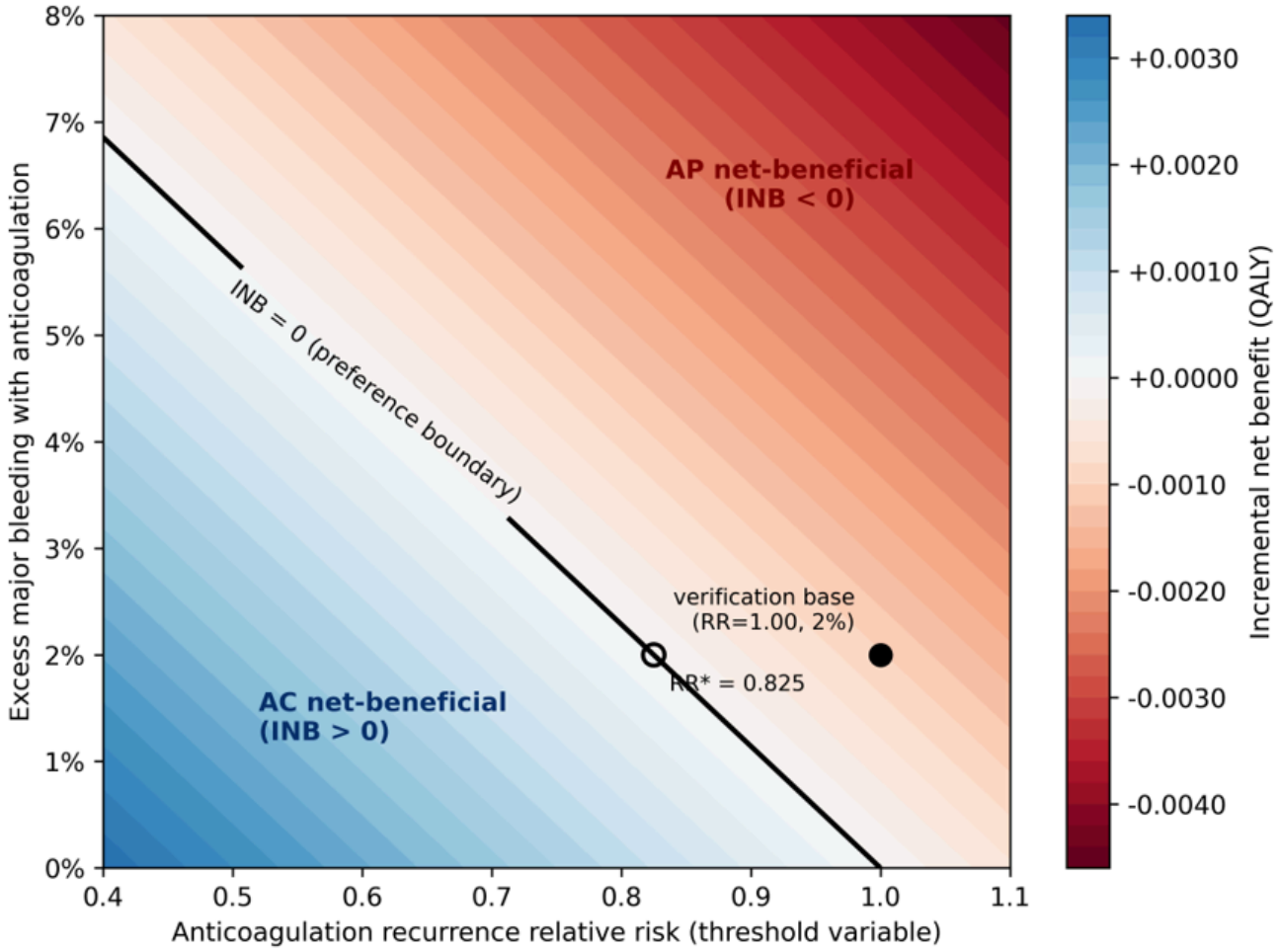


Figure 1

Two-way net-benefit threshold surface. Incremental net benefit (INB) of anticoagulation versus antiplatelet therapy across the anticoagulation recurrence relative risk (x-axis; a threshold variable) and the excess major-bleeding risk (y-axis). The black contour is the strategy-preference boundary (INB = 0): anticoagulation is net-beneficial in the lower-left region and antiplatelet therapy in the upper-right. The filled point marks the deterministic verification base case (RR = 1.00, 2% excess bleeding); the open point marks the recurrence-RR threshold (0.825) at 2% excess bleeding. The surface is a model-based threshold output, not a clinical effect estimate.

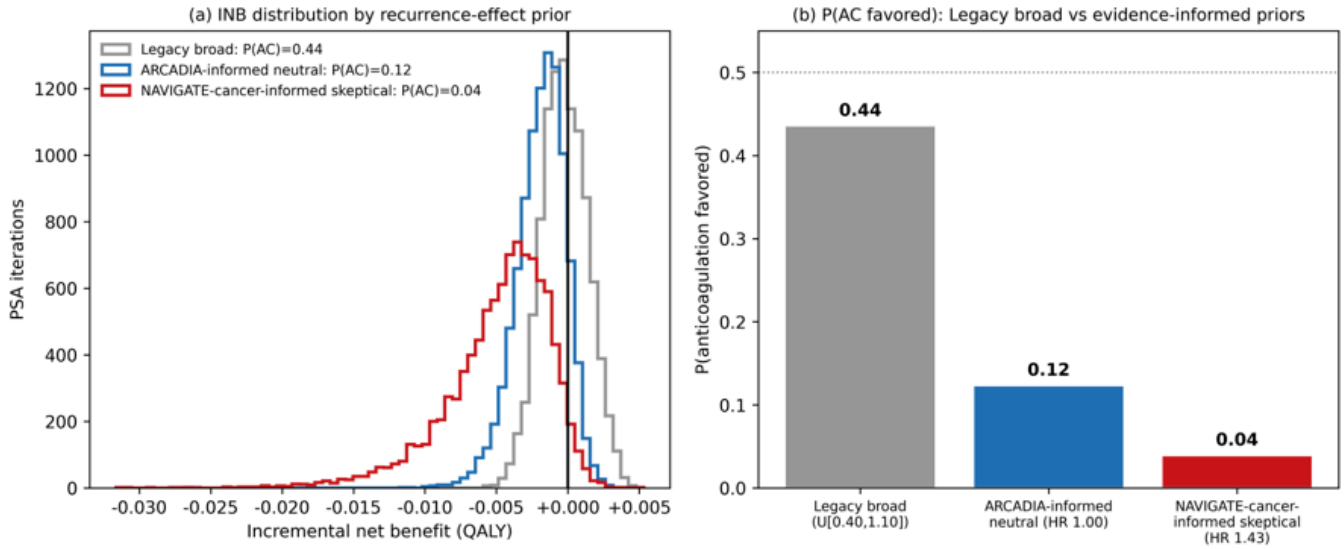


Figure 2

Probabilistic sensitivity analysis under three recurrence-effect priors (N = 10,000; seed 20260613). (a) Distribution of incremental net benefit (anticoagulation minus antiplatelet) under a legacy broad comparison prior (relative risk ~ Uniform[0.40, 1.10]) and two evidence-informed lognormal priors derived from extracted randomized head-to-head estimates — ARCADIA-informed neutral (centred on hazard ratio 1.00) and NAVIGATE-cancer-informed skeptical (centred on hazard ratio 1.43). (b) Probability that anticoagulation is favored, which falls from 0.44 under the legacy broad prior to 0.12 and 0.04 under the evidence-informed priors. Outputs are model-based threshold results, not direct clinical effect estimates.

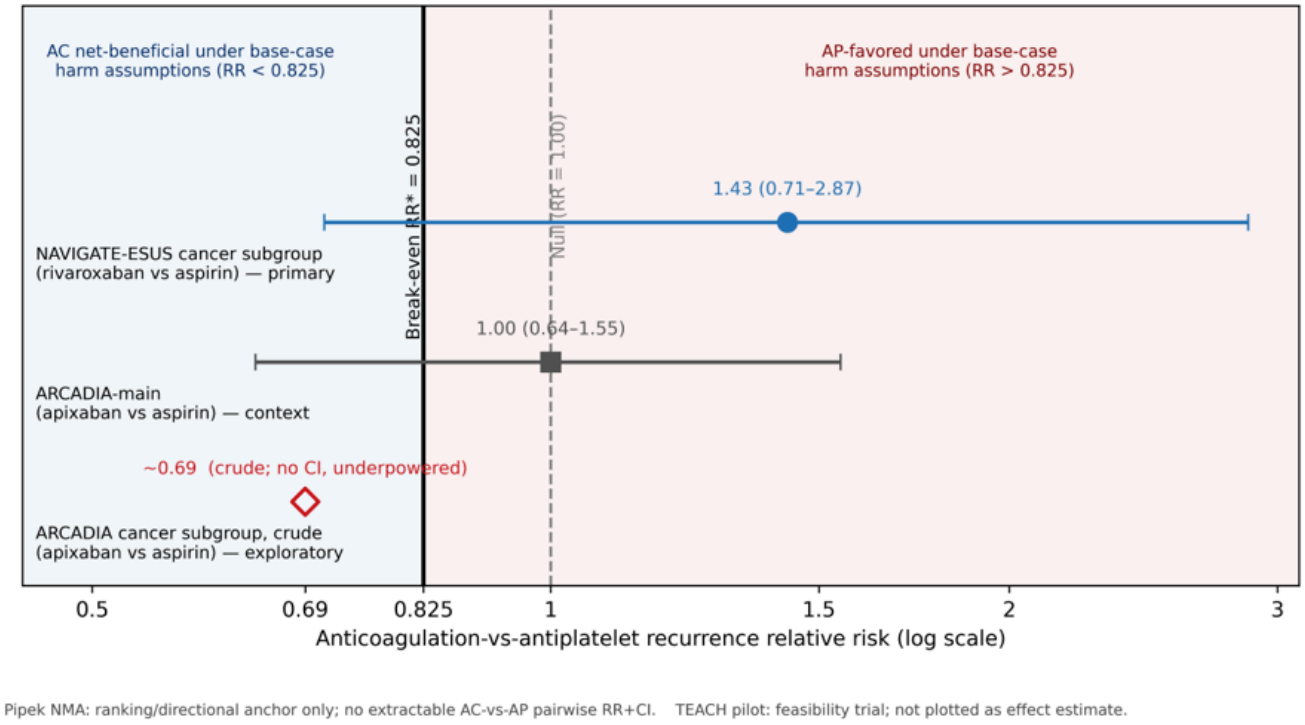


Figure 3

Position of available randomized head-to-head recurrence estimates relative to the model break-even. The break-even recurrence relative risk was 0.825 at the base-case 2% excess major-bleeding assumption. Available randomized head-to-head estimates were wide and indirect; the NAVIGATE-ESUS cancer subgroup (rivaroxaban vs aspirin) and the main ARCADIA trial (apixaban vs aspirin) lay at or above the break-even threshold, whereas the small ARCADIA cancer-history subgroup crude estimate (apixaban vs aspirin) lay below it. These estimates crossed, or lacked precision around, both the break-even threshold and the null (relative risk 1.00), supporting uncertainty rather than anticoagulation superiority. The Pipek network meta-analysis is shown as a ranking/directional anchor only (no extractable anticoagulation-versus-antiplatelet pairwise estimate); the TEACH pilot was a feasibility trial and is not plotted as an effect estimate. Regions are defined under base-case harm assumptions.

Supplementary Files

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