Eliquis Dose Model

Model card for clinical review. Companion to the Healthy Skepticism paper “Eliquis and Its Dose”. Murray Cantor, 2026.

What it is

A Bayesian network for apixaban dosing in atrial fibrillation with the dose as the intervention node (5 mg / 2.5 mg / 0 mg twice daily). Pearl’s do-operator severs the prescribing arrows, separating “who gets 2.5 mg” (a fact about prescribing) from “what 2.5 mg does” (a fact about the drug), and the comparison that matters to a patient is against not taking the drug, not against warfarin. Every parameter traces to a published number; inference is exact enumeration; everything is inspectable and editable (plain Python, ~1,200 lines, plus a formula-only Excel front end).

Structure

Sex, Age, Weight, Creatinine determine CrCl (Cockcroft-Gault). Relative exposure e = (dose/5 mg) x renal multiplier (1.00 / 1.10 / 1.25 / 1.37 by CrCl band; capped by apixaban’s ~27% renal clearance). Stroke risk: observed on-treatment band rates scaled by a Weibull retained-effect curve RR(e) = RR_full^F(e), an AF-burden curve g(b), and a prior-stroke multiplier. Bleeding: the same machinery with its own learned curve, split into ICH (dose-flat) and extracranial (all the dose response). Dose-response, bleeding, and burden curves are grid posteriors learned from the anchors below (Gaussian likelihoods on the log rate-ratio scale — Eddy-style evidence synthesis); every output reports the posterior mean and 5–95% band. Where anchors disagree (PCORnet’s null vs ENGAGE’s dose effect; ENGAGE’s bleeding gradient vs AVERROES’s small excess), the posterior carries the tension as width rather than resolving it by fiat.

Evidence anchors

What it constrains	Anchor and source
On-treatment stroke/SE and major bleeding by CrCl band	ARISTOTLE renal subgroups (Hohnloser 2012); apixaban-arm bleeding via 2.13/2.61 arm ratio (Granger 2011). Reproduced exactly at do(5 mg).
Full-dose effect vs no treatment	AVERROES HR 0.45 vs aspirin (Connolly 2011) x aspirin RRR 22% vs placebo (Hart 2007): RRR ~65%, ln-scale SE 0.26 (90% band 46-77%), carried as a posterior dimension.
Stroke dose-response shape F(e)	Zeitouni 2020 (2.5 mg consistency); Gouda 2026 PCORnet null (aHR 1.05, SE inflated for confounding); ENGAGE 30 vs 60 mg and the low-intensity-warfarin era as class anchors, SEs widened.
Bleeding dose-response shape and magnitude	RE-LY 110 vs 150 mg (2.71/3.11 %/yr) and ENGAGE 30 vs 60 mg (1.61/2.75) as class shape anchors; AVERROES magnitude 1.4 vs 1.2 %/yr (HR 1.13, CI 0.74-1.75; SE inflated - baseline is aspirin).
ICH vs extracranial split	ICH = 15.5% of major bleeds on 5 mg (ARISTOTLE 0.33/2.13 %/yr); held dose-flat because AVERROES found apixaban ICH = aspirin ICH (0.4 vs 0.4 %/yr, HR 0.85, CI 0.38-1.90).
AF burden curve g(b)	ARISTOTLE paroxysmal vs persistent (0.98 vs 1.52 %/yr, EHJ 2013); KP-RHYTHM top burden tertile aHR ~3.1 (Go 2018); ARTESiA subclinical baseline (Healey 2023).
Prior stroke / TIA	Easton 2012 (ARISTOTLE subgroup, 19% prevalence): stroke x2.44 (2.46 vs 1.01 %/yr), bleeding x1.43 (2.84 vs 1.98); drug effect consistent (interaction p 0.71 / 0.69).
Severity weights (death or severe disability)	ICH 0.76, extracranial 0.03 (Fang 2007); stroke from 30-day mortality 19.6% on / 27.7% off anticoagulant (Fang 2012 ATRIA) plus an assumed 35% disability share among survivors.

Calibration and validation

Calibrated: do(5 mg) reproduces the observed ARISTOTLE band rates exactly, per posterior draw; untreated baselines are backed out per draw. Checks the model was NOT fitted to: share on 2.5 mg is 5.4% under the label’s 2-of-3 rule (observed 4–5% in ARISTOTLE) and 13.5% under real-world prescribing (observed 15.4% in PCORnet). Example (80+, >60 kg, Cr 1.5–2.0, %/yr): stroke 2.10 [1.89–2.27] on 5 mg, 2.34 [1.95–2.89] on 2.5 mg, 5.83 [3.64–8.60] untreated; major bleeding 3.94 / 3.06 [2.36–3.85] / 2.47 [1.77–3.37]; fatal-or-disabling composite 1.57 / 1.66 / 3.61.

Assumptions to challenge

Class exchangeability for the RE-LY / ENGAGE / low-intensity-era anchors (SEs widened, not exempted). Separability: the drug’s relative effect is taken as independent of burden and prior-stroke status (licensed by interaction nulls), and those two multipliers as independent of each other. ICH dose-flatness rests on one wide CI. Age acts only through CrCl — no independent age effect given the band. Annual probabilities; no time dimension, competing mortality, or recurrence. CrCl < 25 is outside the trial evidence. The stroke disability share (35% of survivors) is the one unverified severity weight. Each of these is a visible line in the parameters block: to disagree is to edit the line and rerun.

Sources: Granger 2011; Connolly 2011 (AVERROES); Connolly 2009 (RE-LY); Giugliano 2013 (ENGAGE); Hohnloser 2012; Hart 2007; Zeitouni 2020; Gouda 2026; Easton 2012; Al-Khatib 2013 (EHJ, AF type); Go 2018 (KP-RHYTHM); Healey 2023 (ARTESiA); Fang 2007, 2012; Jones 1998 (NHANES III); Pearl 2009.