

Anticoagulation Timing After AF-Related Stroke

The Clinical Dilemma: Competing Risks

Early Ischemic Risk

High risk of recurrent stroke (up to 1-2% per day) in first 0-14 days

Recurrence often disabling or fatal

Drives the need for **early** anticoagulation

Early Hemorrhagic Risk

Infarcts are prone to hemorrhagic transformation (HT)

Risk highest in large infarcts and early time points

Drives the fear of **early** anticoagulation



Balancing Competing Risks

Evolution of Evidence

IPD Meta-Analysis (CATALYST)

Individual RCTs (ELAN, TIMING, etc)

Observational Studies (e.g., RAF Study)

Expert Opinion / Dogma (e.g., "1-3-6-12 Rule")

Four RCTs

Study (N)	Primary Outcome (Time)	Design	Early Arm Protocol	Late Arm Protocol	Primary Result (Early vs. Late)
TIMING (888)	Rec. Stroke, sICH, All-Cause Mort. (90d)	Non-Inferiority (2.5%)	≤4 days (Pragmatic)	5-10 days (Pragmatic)	6.89% vs 8.68% (NI Met)
ELAN (2013)	Rec. Stroke, Sys. Emb., Major EC Bleed, sICH, Vasc. Death (30d)	Superiority	Imaging-based (≤48h or 6-7d)	Imaging-based (3-4d or 12-14d)	2.9% vs 4.1% (p=0.14)
OPTIMAS (3621)	Rec. Stroke, sICH, Unclass. Stroke, Sys. Emb. (90d)	Non-Inferiority (2.0%)	≤4 days (Pragmatic)	7-14 days (Pragmatic)	3.3% vs 3.3% (NI Met)
START (200)	Ischemic or Hemorrhagic Event (30d)	Adaptive Bayesian	Day 3-4	Day 6, 10, or 14	1.9% vs 5.7% / 4.3% / 4.3%

CATALYST: Primary Outcome (30 Days)

Primary Composite: Rec. Ischemic Stroke, sICH, or Unclassified Stroke

Early ($\leq 4d$): 2.1% (57/2683) vs. Later ($\geq 5d$): 3.0% (83/2746)

Absolute Risk Reduction (ARR)

0.9%

NNT: 111

Relative Risk Reduction (RRR)

30%

OR: 0.70 (95% CI 0.50–0.98; p=0.039)

CATALYST: Key Efficacy & Safety Outcomes (30-Day)



Benefit driven by ischemic stroke reduction ($p=0.029$). No significant difference in sICH ($p=0.96$) or mortality ($p=0.19$)

Clinical Application: Exclusions & Protocols

STOP: Evidence Does NOT Apply To:

- Parenchymal Hematoma Type 2 (PH-2)
- Malignant Infarct (e.g., >2/3 MCA, planned hemicraniectomy)
- Suspected Septic Embolism
- Uncontrolled Hypertension (>185/110)
- Patients requiring Warfarin

Pragmatic Protocol

- (CATALYST / TIMING / OPTIMAS)
- For all eligible patients (Mild, Mod, Sev)
- Initiate DOAC \leq 4 Days

Nuanced Protocol

- (ELAN-based)
- **Minor/Moderate Infarct:** \leq 48 Hours
- **Major Infarct:** Day 6-7

CATALYST: Pooled Patient Profile (N=5,441)

Median Age	77.7 (SD 10.0)
Median NIHSS	5 (IQR 3–10)
NIHSS Distribution	0–4 (Mild): 42.8%
	5–10 (Moderate): 32.1%
	≥11 (Severe): 24.4%
On OAC at Onset	32.7%
Reperfusion Therapy	32.5%
Baseline HT (ELAN Substudy)	12.6% (HI-1, HI-2, or PH-1)

Nuance: 30-Day vs. 90-Day Primary Outcome

Primary Outcome at 30 Days

OR 0.70 (95% CI 0.50–0.98)

p = 0.039

Statistically significant reduction

Primary Outcome at 90 Days

OR 0.88 (95% CI 0.65–1.19)

p = 0.40

No significant difference

- *Benefit of early initiation is "front-loaded" in the highest-risk period*
- *After acute phase, both groups are on effective prevention, diluting the treatment effect over time*

Nuance: Functional Outcomes (90-Day mRS)

ELAN (N=2,013)

Good Outcome (mRS 0–2):

62.6% (Early) vs. 62.6% (Late)

Ordinal Shift (mRS 0–6):

adj. OR 0.93 (95% CI 0.79–1.09; p=0.38)

OPTIMAS (N=3,621)

Good Outcome (mRS 0–2):

52.8% (Early) vs. 52.5% (Late)

Ordinal Shift (mRS 0–6):

adj. OR 1.00 (95% CI 0.90–1.12; p=0.96)

- *No significant difference in 90-day mRS (disability) from the *index stroke**
- *Benefit of early DOAC is prevention of *new* recurrent strokes*

Nuance: Subgroup Consistency (p-interaction)



Severe Stroke (NIHSS ≥11)

No evidence of harm; benefit consistent (p-interaction=0.54)



Baseline HT (HI-1, HI-2, PH-1)

No evidence of harm; benefit consistent (p-interaction=0.61)



Stroked While on OAC

No evidence of harm; benefit consistent (p-interaction=0.89)

- *High p-interaction (>0.10) suggests treatment effect is consistent across subgroups*
- *Data provides reassurance for initiating DOACs in these "gray zone" patients*

Radiographic Subgroups



- **Hemorrhagic Transformation (HT):**

All trials excluded Parenchymal Hematoma Type 2 (PH-2)

ELAN substudy (N=1933): 12.6% had baseline HT (HI-1, HI-2, or PH-1)

No harm associated with early initiation in this group (p-interaction=0.61)



- **Infarct Size:**

ELAN substudy: Analyzed outcomes by radiographic size criteria

Benefit of early initiation consistent across Minor, Moderate, and Major infarcts (p-interaction=0.81)

Methods

Trial-Level Data & Meta-Analysis Methods

Trial-Specific: Definitions of Severity

Trial	Method	Mild	Moderate	Severe / Major
ELAN	Imaging-Based (per text)	Infarct \leq 1.5 cm	Infarct in distribution of a cortical superficial branch of MCA, ACA, or PCA	Larger infarcts in these arteries, or brain-stem/cerebellar infarct $>$ 1.5 cm
OPTIMAS	NIHSS-Based (Stratification)	0-4	5-10 / 11-15	16-21 / $>$ 21
TIMING	NIHSS-Based (Subgroups)	0-3	4-5 / 6-10	11-15 / $>$ 15
START	NIHSS/Imaging (Exclusion)	Enrolled NIHSS 0-23		Excluded if NIHSS $>$ 23 or $>$ 50% MCA territory

Trial Analysis: ELAN (N=2,013)

Design & Population

- **Design:** Open-label, superiority trial
- **Population:** AF-stroke <100h; Median NIHSS=3 (IQR 1-6)
- **Key Exclusions:** PH-1 / PH-2, planned surgery
- **Intervention:** Imaging-based stratification
 - **Minor/Mod:** ($\leq 48\text{h}$) vs (Day 3-4)
 - **Major Infarct:** (Day 6-7) vs (Day 12-14)
- **Limitations:**
 - Excluded patients on therapeutic AC
 - Low median NIHSS (Median 3)
 - Excluded PH-1 and PH-2
 - Primary superiority endpoint not met

30-Day Outcomes

Outcome	Early (N=1006)	Late (N=1007)	OR (95% CI); p-value
Primary Composite	2.9%	4.1%	0.70 (0.44-1.14); p=0.14
Recurrent Ischemic Stroke	1.4%	2.5%	0.57 (0.29-1.07)
Symptomatic ICH	0.2%	0.2%	1.02 (0.16-6.59)

Trial Analysis: TIMING (N=888)

Design & Population

- **Design:** Pragmatic, non-inferiority (NI Margin 2.5%)
- **Population:** AF-stroke; Median NIHSS=4 (IQR 2-8)
- **Key Exclusions:** PH-2, "very large" infarcts (investigator discretion)
- **Intervention:** Pragmatic time-based
 - **Early Arm:** Start DOAC \leq 4 days
 - **Late Arm:** Start DOAC 5-10 days
- **Limitations:**
 - Terminated early (N=888 of 3000 planned); underpowered
 - Wide confidence intervals
 - No standardized central imaging
 - Subjective exclusion of "very large" infarcts

90-Day Outcomes

Outcome	Early (N=450)	Late (N=438)	Risk Diff (95% CI); p-value
Primary Composite	6.89%	8.68%	-1.79% (-5.31 to 1.74); p(NI)=0.004
Recurrent Ischemic Stroke	3.11%	4.57%	-1.46% (-3.98 to 1.07)
Symptomatic ICH	0.0%	0.0%	N/A

Trial Analysis: OPTIMAS (N=3,621)

Design & Population

- **Design:** Pragmatic, non-inferiority (NI Margin 2.0%)
- **Population:** AF-stroke <72h; Median NIHSS=4 (IQR 2-7)
- **Key Exclusions:** PH-2, infarct >2/3 MCA, planned hemicraniectomy
- **Intervention:** Pragmatic, later control arm
 - **Early Arm:** Start DOAC ≤ 4 days
 - **Late Arm:** Start DOAC 7-14 days
- **Limitations:**
 - Protocol leaves data gap (days 4-7)
 - Low power for sICH (n=23 total)
 - Few severe strokes (NIHSS >21) enrolled
 - Excluded PH-2, limiting guidance

90-Day Outcomes

Outcome	Early (N=1814)	Late (N=1807)	Adj. Risk Diff (95% CI); p-value
Primary Composite	3.3%	3.3%	0.000 (-0.011 to 0.012); p(NI)=0.0003
Recurrent Ischemic Stroke	2.4%	2.3%	-0.001 (-0.011 to 0.009)
Symptomatic ICH	0.6%	0.7%	0.001 (-0.004 to 0.006)

Trial Analysis: START (N=200)

Design & Population

- **Design:** Adaptive Bayesian (to find *optimal* time)
- **Population:** AF-stroke; Median NIHSS=6.5 (IQR 4-14)
- **Key Exclusions:** NIHSS >23, infarct >50% MCA, ***any* HT (HI-1, HI-2, PH-1, PH-2)**
- **Intervention:** Multiple arms
 - Day 3-4 vs. Day 6 vs. Day 10 vs. Day 14
- **Limitations:**
 - Terminated early (N=200); low power
 - High loss to follow-up (10% at 30d)
 - Potential selection bias (slow enrollment)
 - Excluded *all* HT, limiting generalizability

30-Day Primary Outcome

Arm	Event Rate (%)
Day 3-4 (N=54)	1.9% (1 event)
Day 6 (N=53)	5.7% (3 events)
Day 10 (N=46)	4.3% (2 events)
Day 14 (N=47)	4.3% (2 events)

Methods

Statistical Model

- One-stage IPD meta-analysis
- Generalized linear mixed-effects model
- Random effect for trial (handles clustering)
- Patient-level covariate adjustment

Trial Design & Adjudication

- All 4 trials: PROBE design (Open-Label, Blinded Endpoint)
- Central, blinded re-adjudication of all primary endpoints
- Standardized definitions applied

Data Harmonization

- **Early Arm:** Initiation ≤ 4 days
- **Later Arm:** Initiation ≥ 5 days
- Harmonized split based on TIMING & OPTIMAS pragmatic design

CATALYST: Statistical Robustness



Per-Protocol Analysis (N=5,110)

Result consistent: OR 0.69 (95% CI 0.49–0.98), p=0.037



Two-Stage Meta-Analysis

Result consistent: OR 0.70 (95% CI 0.50–0.98), p=0.040



Leave-One-Out Analysis

Removing TIMING: OR 0.69 (0.48–0.99)

Removing ELAN: OR 0.83 (0.54–1.28)

Removing OPTIMAS: OR 0.61 (0.39–0.97)

Removing START: OR 0.70 (0.49–0.99)

Major Methodological Biases & Confounders



Open-Label Design (All Trials)

Potential for performance bias; mitigated by PROBE (blinded endpoint adjudication)



Protocol Heterogeneity (Meta-Analysis)

Combining dissimilar trial designs (imaging-based vs. pragmatic)

Varied control arm definitions (e.g., 5-10d, 7-14d, 12-14d)



Antiplatelet Bridging (Confounder)

Active treatment in the "Later" arms biases results toward the null



Selection Bias (All Trials)

Exclusion of highest-risk patients (PH-2, malignant infarcts) limits generalizability



Early Termination (TIMING, START)

Trials were underpowered; risk of unstable/biased effect estimates

Methodological Note: Antiplatelet "Bridging"

- ⌚ **Heterogeneous Protocols:** No uniform protocol for antiplatelet (AP) use in the "gap" period
- ⌚ **Confounding Variable:** Many patients in "Later" arms received AP therapy (mostly aspirin) while awaiting DOACs
- 📊 **Biostatistical Implication:** Use of an active comparator in the "Later" arm likely biases results toward the null

Methodological Note: DOAC Choice & Dosing



Pragmatic Choice: Trials did not mandate a specific DOAC

TIMING (N=888): Apixaban (55%), Dabigatran (28%), Rivaroxaban (13%), Edoxaban (3%)

OPTIMAS (N=3621): Apixaban (62%), Edoxaban (29%), Rivaroxaban (5%), Dabigatran (2%)



Dosing: ~25% received reduced DOAC dose, consistent with labeling



Subgroup Finding: No significant interaction by DOAC choice ($p\text{-interaction}=0.37$)

Remaining Uncertainties & Future Directions

PH-2 & Malignant Infarcts

- Parenchymal Hematoma Type 2 (PH-2) universally excluded
- Patients needing hemicraniectomy excluded
- Timing in this high-risk group remains unknown



Warfarin Patients

- Data is DOAC-only
- No evidence for patients requiring Warfarin (e.g., mechanical valves, APLAS, severe CKD)



Septic Embolism

- Evidence applies *only* to AF-related stroke
- *Cannot* be applied to suspected septic embolism from endocarditis



Future: < 24 Hours?

- "Early" arm (≤ 4 days) does not define optimal time *within* that window
- **ASAP Trial (NCT06057467):** Ongoing RCT testing 0-24h vs. 3-4 days in mild-moderate stroke (NIHSS 0-15)

Totality of Evidence

Cumulative IPD evidence (N=5,441) supports DOAC initiation within 4 days for AF-stroke (without PH-2). This strategy reduces the 30-day composite outcome, driven by a 30% RRR in ischemic stroke, with no significant increase in sICH.