Restarting Anticoagulation after Intracranial Hemorrhage

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sICH vs tICrH

Not the same disease
Spontaneous intracerebral hemorrhage occurs in the brain parenchyma due to abnormal, fragile vasculature, caused by amyloid deposition in arteriolar walls, and/or microvascular injury from poorly controlled hypertension.

Traumatic intracranial hemorrhage, the vasculature is usually normal. Trauma moves the brain violently within the cranium; either the tensile strain within the brain overcomes vascular resistance at a given point, leading to hemorrhage, or a concentration of shock waves secondary to impact causes mechanical disruption of blood vessels.
Should we restart anticoagulation?

Yes/No Trials in sICH ongoing

In tICrH, question is usually when not if

Several other TICrH studies show reductions in stroke with restart, with variation in rebleeding. Many found better long-term survival with restart, especially in high-risk atrial fibrillation patients.

Low quality evidence!

Restart Ischemic Stroke Reduction 51% in sICH and 60% in tICrH

*Warfarin Data
Should we restart?

Observational data suggests 1:10 ratio
Risk benefit should lie between 1:2 if all bleeding is recurrent ICH and all thrombosis is DVT and 1:10 if all bleeding is minor and all thrombosis is stroke
Increasing rebleeding risk
Central Hypothesis

There is a best time for most patients to restart oral anticoagulation after major hemorrhage that optimizes the composite outcome of bleeding and thrombosis.
Secondary risks of restarting AC following a bleeding event

Days to RESTART

Composite

Clot

Bleed

Risk

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Primary outcome interval
Primary Endpoint - Bleeding

Low risk

- Minor Bleeding: 0%
- Clinical Relevant Non major bleed: <1%
  - BARC 2, Clinically actionable

High risk

- Major GI/Other bleed: 10%
  - mBARC 3
- Worsening tICH/new ICH: 20%

Primary Endpoint - Thrombosis

- DVT: 5%
- MI: 15%
- AIS/Systemic embolism: 15%
- PE: 20%

60-day mRS/DRS to inform weights (exploratory)
Trial Design

• Time as a dose
• Response Adaptive Randomization
  • Ethical – more patients in better performing groups without sacrificing power
  • Economical – stops early for futility or clear superiority
Trial Design (n=1100 participants)

- Response adaptive randomization with information formula
- Two endpoints: TE (binary) and Bleeding (binary) within 60 days
- Two separate monotonic Normal Dynamic Linear Models for TE and Bleeding
- Interims: 300, 400, 500, 600, 700, 800, 900, & 1000 (1100 final analysis)
- Comparisons of interest: (1W vs 2W; 1W vs 4W; or 2 W vs 4W)
- Dropout rate 10% (~990 completers)
- Type I error 5%
- Power 86%
- 606 out of 1100 randomized to better arm (fixed trial would be 1100/3=367) (under projected effect sizes)
Figure 7: Restart TICrH is a PROBE response adaptive clinical trial of different time intervals to restart anticoagulation after traumatic intracranial hemorrhage (1). Arm restart days (7, 14, and 28) are illustrated here by the change from blue to red in the horizontal bars, a transition from thrombotic risk to bleeding risk (2), which are the opposing risks combined in the primary composite endpoint. The composite endpoint of major bleeding and thrombotic events (3) is illustrated by the red and blue vertical bars, which reflect the proportions of bleeding and thrombosis and predicted combined rate, with the expected rates used for trial power in the next column. The differences in these composite endpoints by arm drive randomization adaptation (4). The algorithm decreases the probability of randomization to underperforming arms; that is, those with higher event rates. A second adaptive mechanism for the inclusion criteria is driven by total endpoint event rate in all arms (and therefore does not require unblinding) (5). This mechanism enriches the trial population for events by raising the CHA\textsubscript{2}-DS\textsubscript{2}-VASc to prevent the trial from ending for futility \textsuperscript{47}. 
Figure 8: At the first interim we apply prespecified formal decision rules to adapt exclusion criteria for disparate effects by frailty, hematoma volume and thrombotic risk (CHA2DS2-VASc). These analyses are across all groups and do not require unblinding. The CHA2DS2-VASc adjustment is also used to enrich for events if necessary (see Trial Management Plan). The decision rules will be developed and simulated in the UG3 planning year. (TSFI=Trauma Specific Frailty Index $^{39}$)
Restart TICrH Vanguard – a GTRN Study
Vanguard Purpose ($300,000 unrestricted CSL Behring grant)

1. To collect the first prospective randomized data on this important question

2. If the main grant is funded, these patients will be included in the main trial, after DSMB approval.

If it is not funded, we will write this up as a 200-patient pilot trial with all of us as co-authors.
Typical Course
Inclusion Criteria

1. Clinician intent to restart a Direct Oral Anticoagulant (DOAC) after anticoagulant-associated traumatic intracranial hemorrhage and equipoise concerning restart of anticoagulation at the specified time intervals.

2. Acute traumatic intracranial hemorrhage on anticoagulation for Atrial Fibrillation (AF) or Venous Thromboembolism (VTE)

3. Patient is higher risk for stroke or other thrombotic events as witnessed by having a CHA₂DS₂-VASc score of ≥ 3

4. DOAC will be prescribed at label dose with label adjustments for creatinine clearance. DOAC will be at continuation dose, i.e., not initial therapy high doses in the setting of VTE.
Exclusion Criteria

- Mechanical Valve
- Ventricular Assist Device (VAD)
- SDH ≥ 8 mm maximum width or any midline shift at any time point or more than one SDH
- Physician plan to start/restart antiplatelet therapy during trial period
- Abbreviated Injury Scale other than head ≥ 3
- Pregnancy
- Inability to understand need for adherence to study protocol
- Renal function below DOAC label exclusions
- Any active pathological bleeding
- Hypersensitivity to drug or other label contraindication
- Any bleeding that the investigator deems unsafe to restart DOAC at 1 week post injury, or conversely unsafe to hold DOAC to 4 weeks
- Completion of DOAC therapy expected prior to 60-day primary endpoint
- Concomitant need for strong inducers/inhibitors of p-gp and CYP3A4
- Low body weight (≤ 45 kg)
- Inability to swallow
Questions?

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