Restarting Antithrombotic Therapy after Intracerebral Hemorrhage

12th Annual Practical Management of Stroke

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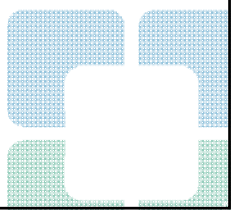
Objectives

- Describe common definitions we use with regards to intracerebral hemorrhage and stroke
- Review the evidence for restarting antithrombotic therapy after primary intracerebral hemorrhage
- List ongoing randomized trials which may help to answer several questions in this area of stroke management

Outline

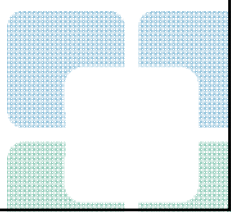
- Definitions
- Overview
- Antiplatelet initiation/re-initiation
- Anticoagulation initiation/re-initiation
- Conclusion



Definitions and Abbreviations

- Intracerebral Hemorrhage (ICH) → bleeding directly into brain parenchyma; subarachnoid hemorrhage (SAH), subdural hematoma (SDH) are other forms of intracranial bleeding
  - For the purpose of this discussion, ICH will be in reference to primary ICH (ie, not caused by an underlying structural abnormality or coagulopathy)

- APT → Antiplatelet therapy
- OAC → Oral anticoagulation
- RCT → randomized controlled trial



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Overview

Why do we care about antithrombotics?

What do we know about preceding antiplatelet use and ICH?

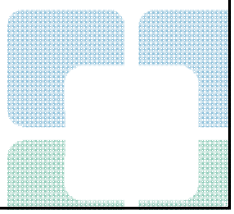
- Preceding use of antithrombotics associated with larger initial hematoma volumes and hematoma expansion[1-3]
- Preceding APT literature varies with some supporting worse prognosis and hematoma expansion, and some without
  - 2010 systematic review (25 cohort studies) showed prior APT use associated with increased mortality (OR 1.3), but not worse functional outcome after ICH[4]
  - More recent prospective study showed prior APT use was associated with increased baseline ICH volume and greater risk of hematoma growth[5]
- PATCH trial[6] → platelet transfusion inferior to standard care for those on APT preceding ICH and should not be given unless pre-op consideration

Overview

Why do we care about antithrombotics?

What is the evidence surrounding anticoagulation use and ICH?

- Preceding OAC mortality rate after ICH 52-73% which is higher than those who are not on any prior to ICH (RR 3-4)
  - Still uncertainty here if this differs among warfarin vs direct oral anticoagulants, though one study found no difference in baseline ICH volume, rate of hematoma expansion, or 3 month functional outcome[7]



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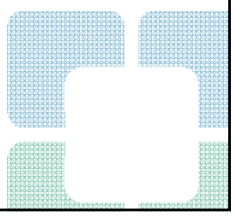
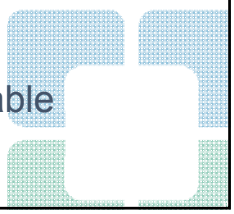


Restarting Antiplatelet Therapy

Overview Thoughts:

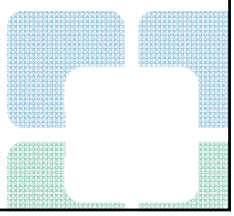
- Risks versus benefits need to be weighed and discussed
- Multi-disciplinary approach can be useful
- Antiplatelet therapy for secondary prevention of cerebrovascular or cardiovascular disease should be used in patients who are at a high risk of future ischemic events and low risk of recurrent ICH
  - Deep ICH, well controlled BP
- Try to avoid APT in patients with prior lobar ICH when able



Restarting Antiplatelet Therapy

RESTART Trial: Effects of antiplatelet therapy after stroke due to intracerebral hemorrhage[8]

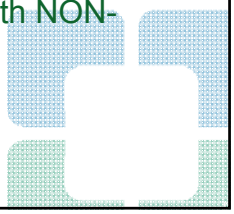
- Prospective, randomized trial at 122 hospitals throughout the UK
- Pre-ICH APT for prevention of occlusive vascular disease
- 1:1 randomization for APT (N=268) vs no APT (N=269)
- Up to physician discretion regarding which APT was used or if mono vs dual therapy used and not well reported in paper



Restarting Antiplatelet Therapy

RESTART Trial: Results

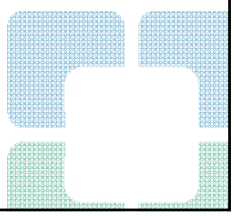
- Primary outcome: recurrent ICH up to 5 years (median f/u 2y)
  - → 4% recurrent ICH APT vs 9% recurrent ICH NO APT
- Secondary: Major hemorrhagic events, major occlusive vascular events, major vascular events
  - → Major hemorrhagic events: 7% APT vs 9% NO APT
  - → Major occlusive vascular events: 15% APT vs 14% NO APT
  - → Major vascular events: 17% APT vs 24% NO APT
- → Restarting APT seems safe; more prominent in patients with NON-lobar ICH



Restarting Antiplatelet Therapy

ASA and Recurrent ICH with Cerebral Amyloid Angiopathy (CAA)[9]

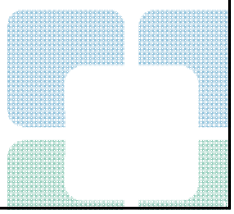
- Characteristics of recurrent ICH
- N=104 lobar ICH
- ASA after ICH NOT associated with lobar ICH recurrence in univariate analysis, but when adjusting for baseline clinical predictors, showed to independently increase the risk of ICH recurrence (HR 3.95)



Restarting Antiplatelet Therapy

TIMING?

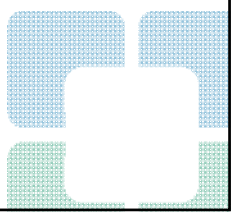
- Greatest risk of hematoma expansion and re-bleeding is within the first several hours after ICH[10,11]
- Re-bleeding and expansion unlikely after 10 days → ?wait 1-2 weeks after ICH to re-start APT
- Consideration of re-starting APT after 48h if imaging stable[12]
- Recommendation to use low-dose ASA[13-15]



Restarting Antiplatelet Therapy

Concluding Thoughts on APT:

- Weighing risks and benefits of antiplatelet therapy and recurrent ICH remains challenging
- It is reasonable to re-start ASA for patients with multiple vascular risk factors and/or prior TIA, ischemic stroke, MI, PAD
- Primary prevention of vascular events with APT should be avoided
- Recurrent ICH patients: APT should be avoided, as able



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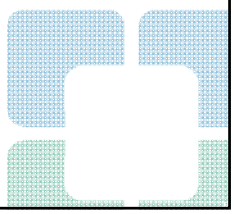
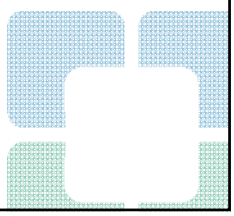


Initiation/Re-initiation of OAC after ICH

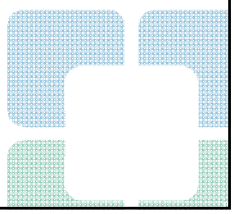
- As with OAC after AIS, no RCTs here or on whether this should be initiated at all, but what do we know? …

- 2017 systematic review and meta-analysis (8 studies) comparing thromboembolic events (stroke, MI) and recurrent ICH[16]
  - Lower risk of thromboembolic events with OAC (though mostly warfarin) WITHOUT increased risk of ICH though had significant heterogeneity=0.28
  - Did not address timing



Initiation/Re-initiation of OAC after ICH

- Ongoing RCTs:
  - APACHE-AF (Netherlands)
  - SoSTART (UK)
  - ASPIRE (US)
  - A3ICH (France)

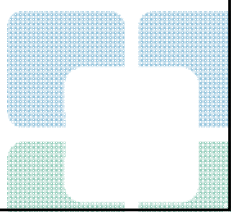


What do the guidelines say?

2015 AHA/ASA Guidelines for ICH[12]

- "Avoidance of long-term anticoagulation with warfarin as a treatment for nonvalvular atrial fibrillation is probably recommended after warfarin-associated spontaneous lobar ICH because of the relatively high risk of recurrence *(Class IIa; Level of Evidence B*)."

- "Anticoagulation after nonlobar ICH and antiplatelet monotherapy after any ICH might be considered, particularly when there are strong indications for these agents *(Class IIb; Level of Evidence B*)."



What do the guidelines say?

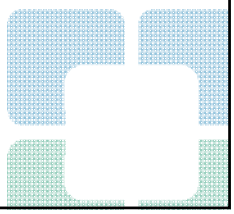
2015 AHA/ASA Guidelines for ICH

- "The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is uncertain. Avoidance of oral anticoagulation for at least 4 weeks, in patients without mechanical heart valves, might decrease the risk of ICH recurrence *(Class IIb; Level of Evidence B*). (New recommendation) If indicated, aspirin monotherapy can probably be restarted in the days after ICH, although the optimal timing is uncertain *(Class IIa; Level of Evidence B*)."

- "The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH to decrease the risk of recurrence is uncertain *(Class IIb; Level of Evidence C*)."

Restarting Anticoagulation Therapy

Do we have any other options, specifically for atrial fibrillation indication? …



Percutaneous LAA Closure

- Up to 91% non-rheumatic AF-related LA thrombi are thought to be isolated to LAA[17]
- Only Watchman device (Boston Scientific; 2005) has been study and approved in US
  - Self-expanding nitinol structure implanted at ostium of LAA
  - Percutaneous approach via femoral vein through RA then transseptal rupture in LA then ultimately LAA (see next slide)
- Standard antithrombotics: warfarin + ASA x45d followed by DAPT x6mo then ASA monotherapy; this is done to ensure seal and endothelialization of device to limit device-related thrombosis; TEE confirms at 45d and repeated at 6mo if leak >5mm[18]

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Percutaneous LAA Closure

- PROTECT AF (2009)[19:] multicenter, controlled, noninferiority trial of pts with NVAF to Wathcman LAA closure vs warfarin; n=707
  - Watchman was noninferior for rate of AIS/ICH/CV death/systemic embolism (3 events/100patient-years vs 4.9 warfarin)
  - Less hemorrhagic strokes in device group (1 vs 6)
  - Increased rate of pericardial effusions in device group
- PREVAIL trial (2014)[20:] randomized 407 patients with NVAF to Wathcman vs warfarin
  - Lower rate of pericardial effusions compared to PROTECT (thought to be d/t more experienced proceduralists)
  - Noninferior in rate of stroke/systemic embolism from 7d-18mo though not in CV death or systemic embolism at 18mo thought to be d/t low rates in warfarin group

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Percutaneous LAA Closure

- Meta-analysis of 5 year combined outcomes from PROTECT AF and PREVAIL (2017)[21]
  - Watchman reduced cardiovascular and all-cause mortality
  - Equal rates of ischemic strokes
  - Reduction in hemorrhagic and disabling/fatal strokes
- 2 registries (CAP, CAP2) following PROTECT AF and PREVAIL patients longer confirmed original trial results though slightly increased A/Es thought to be d/t more severe comorbidities in device groups[22]
- DRT 3.74% pooled analyses of all 4 studies above and predictive of stroke/systemic embolism

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Percutaneous LAA Closure

- **ASAP study (2013)[23]**: single-arm multicenter nonrandomized study of Watchman with DAPT x6mo without warfarin at all then ASA monotherapy
  - 1.2y mean f/u
  - Annual ischemic stroke rate 1.7% (calculated to be 77% fewer strokes than ASA and without Watchman based on risk)
  - More recent 5y f/u → 1.8% annual risk stroke/systemic embolism which was similar to device arms in PROTECT-AF and PREVAIL (1.6%)[23,24]
- **EWOLUTION trial (2019)[25]**: single-arm multicenter, prospective, nonrandomized trial to look at real-life 2y Watchman outcomes; n=1,020
  - 72% only antiplatelets (no warfarin) and 84% of those monotherapy
  - 1.3 strokes/100 person years (83% reduction compared to no-device)
  - DRT 4.1%
  - Overall lower bleeding risks

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Percutaneous LAA Closure

- Based on ASAP/EWOLUTION → European Heart Rhythm Assoc. experts recommend DAPT 1-6mo as possible alternative for pts who absolutely cannot be on warfarin and DOACs could be considered[26]
- US has not yet adapted above
- ASAP-TOO: currently underway to look at Watchman in patients ineligible for OAC[27]
- Other devices
  - PLAATO 2001 (first)
  - 6 others approved in Europe

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Surgical LAA Closure

- Completely exclude LAA
- Ligation, suture, staple, clip
- Usually done in patients undergoing cardiac surgery for other indication
- Retrospective studies have shown reduced post-op thromboembolism rates with concomitant LAA closure during surgery[28,29]
- Small randomized trial compared internal ligation, staple, surgical excision → surgical incision best[30,31]
- Surgical closure has high incomplete rates (sometimes close to 50%), need post-op TEE

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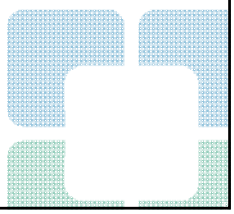
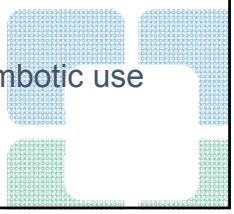


Key Takeaways

- Initiation/re-initiation of antithrombotic therapy after ICH is controversial, and there is limited literature here to guide us, specifically with OAC
- Blood pressure control remains paramount in reducing risk of primary ICH and recurrent ICH and should be a focal point of preventative treatment; this is especially true when considering initiation/re-initiation of antithrombotic therapy
- For patients with atrial fibrillation, consideration of left atrial appendage closure should be considered in those with long-term high risk for recurrent ICH
- Hopefully ongoing RCTs will help guide management of antithrombotic use in patients with history of ICH in the near future



Questions?

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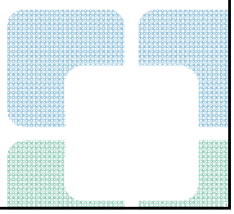

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Every life deserves world class care.