Anticoagulation in ICH Survivors for PreventIon and REcovery (ASPIRE)

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Resumption of Oral Anticoagulation after Intracerebral Hemorrhage is Associated with Decreased Mortality and Favorable Functional Outcome

Biffi et al, *Ann Neurol*, 2017

Background

- As many as 20% of ICH survivors have or develop atrial fibrillation. This subset faces an especially high risk for ischemic stroke and poor outcome.
- In patients with AF and a CHA_2DS_2-VASc score ≥ 2, treatment with oral anticoagulants (OAC) is a IA recommendation from the AHA
- In all OAC studies of "newer" agents, which have improved safety profiles, ICH patients have been excluded

ICH and Oral Anticoagulation

Intracerebral Hemorrhage (ICH) related to **Oral Anticoagulation Treatment (OAT)**:

- ~ 80% cases with atrial fibrillation → high ischemic stroke risk
- underlying small vessel disease → high re-bleeding risk

Resumption of oral anticoagulation is a major clinical dilemma in ICH care

Currently available evidence:

Thrombosis Risk
- CNS: ischemic stroke
- Systemic Thromboembolism

Hemorrhage Risk
- CNS: recurrent ICH
- Systemic Bleeding

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Mortality

AHA ICH Guidelines (2015)

- "Anticoagulation and antiplatelet therapy after non-lobar ICH might be considered" (IIb, B)
- "The usefulness of dabigatran, rivaroxaban, or apixaban in patients with atrial fibrillation and past ICH is uncertain" (IIb, C)
- "An important question to be addressed is the possible role of the newer direct OAC's in patients at increased ICH risk and the identification of the subgroup that might derive the greatest benefit from the tendency of these agents to trigger recurrent bleeding"

OAT Resumption and Outcome

- Thrombosis and/or hemorrhagic events affect patients based on **both long-term impact disability and mortality**

OVERALL STUDY GOAL (2)
Focus on **functional status** as outcome of OAT resumption after ICH

- **Primary outcome: Modified Rankin Scale (mRS): 0-3 at 1 year**
- **Additional outcomes** of interest (at 1 year):
  - Mortality
  - Recurrent ICH
  - Ischemic Stroke

Study Design and Methods

- **Meta-analysis of individual-level data from three ICH studies:**
  1. RETRACE study (multi-center), Germany (n = 542)
  2. MGH ICH study (single center), Boston USA (n = 268)
  3. ERICH study (multi-center), USA (n = 217)
- Inclusion Criteria:
  1. acute ICH (CT-confirmed)
  2. age 18 years or older
  3. history of non-valvular atrial fibrillation
  4. on OAT with VKA/NOAC
  5. no history of prior ICH (high re-bleeding risk)
- Statical methods:
  - Univariable and mulivariable analyses in each study
  - Meta-analysis (random effects) to combine individual studies

Participants' Characteristics

	RETRACE		MGH		ERICH	
	Lobar ICH	Non-lobar ICH	Lobar ICH	Non-lobar ICH	Lobar ICH	Non-lobar ICH
No. subjects	202	340	106	162	78	139
Age (years)	74.7 (7.9)	74.6 (7.8)	73.4 (10.8)	70.2 (9.9)	73.8 (11.1)	71.3 (12.0)
Sex (male)	119 (59)	211 (62)	51 (48)	99 (61)	46 (59)	76 (55)
ICH Volume	26.9 (10.5 - 56.0)	10.2 (4.8 - 22.0)	27.3 (11.0 - 57.4)	11.2 (4.6 - 21.9)	18.4 (6.2 - 43.7)	6.2 (1.6 - 15.8)
OAT Resumption	38 (19)	72 (21) ↑	38 (36)↑	74 (46)↑↑	12 (15)	33 (24)↑

OAT Resumption and Outcomes

Non-lobar ICH

Outcome at 1 Year	Effect of OAT Resumption		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	4.41	2.92-6.67	**<0.0001**
Mortality	0.26	0.17-0.39	**<0.0001**
All-cause Stroke	0.45	0.28-0.71	**0.0008**
- Recurrent ICH	1.12	0.94-1.34	0.22
- Ischemic Stroke	0.42	0.22-0.81	**0.011**

Lobar ICH

Outcome at 1 Year	Effect of OAT Resumption		
	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	4.15	2.81-6.13	**<0.0001**
Mortality	0.29	0.20-0.42	**<0.0001**
All-cause Stroke	0.51	0.32-0.80	**0.004**
- Recurrent ICH	1.26	0.99-1.60	0.059
- Ischemic Stroke	0.48	0.27-0.85	**0.013**

OAT and Possible vs. Probable CAA

Possible CAA (n=137)

Outcome at 1 Year	Unadjusted			Adjusted		
	HR	95% CI	p	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	3.44	1.16-10.22	**0.027**	3.40	1.22-9.46	**0.020**
Mortality	0.21	0.05-0.89	**0.034**	0.27	0.08-0.86	**0.028**

Probable CAA (n=55)

Outcome at 1 Year	Unadjusted			Adjusted		
	HR	95% CI	p	HR	95% CI	p
Favorable Outcome (mRS 0 -3)	3.33	1.03-10.77	**0.046**	3.11	1.08-8.97	**0.038**
Mortality	0.28	0.09-0.91	**0.035**	0.30	0.10-0.92	**0.037**

Conclusions

- **OAT resumption after both lobar and non-lobar ICH** was associated with the following outcomes at 1 year:
  - Improved functional outcome
  - Decreased mortality risk
  - Decreased ischemic stroke risk
- **OAT resumption after ICH due to possible / probable CAA** was associated with decreased mortality and improved outcome

Limitations:

- Observational study framework
- Follow-up limited to one year
- Very few patients on NOAC

- Future Directions: findings support and offer design guidance for **clinical trials of OAT resumption and outcome after ICH**

Innovation

Objective

The primary aim of this trial will be to test the hypothesis that apixaban is superior to aspirin for reducing the rate of recurrent stroke (ischemic or hemorrhagic) or death.

The key secondary outcome of this trial will test the hypothesis that apixaban is superior to aspirin for improved functional outcome as measured by the modified Rankin Scale.

Intervention

Intervention: Randomized double blind RCT – Apixaban 5 mg po bid versus aspirin 81 mg po qd for one year post-randomization

Inclusion/Exclusion Criteria

Inclusion Criteria

- ICH, documented with CT or MRI
- ICH must have occurred in the 14-120 days months prior to randomization
- Diagnosis of non-valvular AF, documented on electrocardiography or history

Exclusion Criteria

- Lobar ICH and ≥ 5 lobar microhemorrhages
- Conditions other than AF for which the patient requires long term anti-coagulation (e.g., deep venous thrombosis)
- A different clinical indication for the use of an anti-platelet drug even if treated with apixaban, such as clopidogrel for recent coronary stenting
- Chronic kidney disease with serum creatinine ≥2.5 mg/dL

Miscellaneous

- A total of 700 subjects across 125 sites for 85% power to detect a hazard ratio of 0.6
- ASPIRE will be a 5 year study, with 3.5 years of enrollment and at least 1 year of follow up for all patients
- We will collect and bank blood and imaging for ancillary and secondary analyses where possible
- We are participating in the international COCHROACH collaboration and organizing a pre-pooled patient level meta-analysis of global trials on this question

Steering Committee and Partners

- Steven Greenberg
- Walter Kernan
- Jonathan Rosand
- David Tirschwell
- Daniel Woo
- Study Statistician – Jordan Elm
- NCC, DCC, Claudia Moy, Scott Janis
- Medical Safety Monitor – Alejandro Rabinstein
- Chair, Adjudication Committee – Wendy Ziai