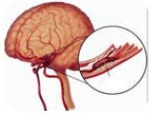
Combination Antithrombotic Therapy for reduction of recurrent Ischemic Stroke in patients with IntraCranial Atherosclerotic Disease

CATIS-ICAD



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Background and Rationale

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- ICAD accounts for 8-10% of ischemic strokes in Caucasians

Main ICAD trials:

- **WASID:** Warfarin-ASA Symptomatic Intracranial Disease. ICAD (50-99%)
- Primary outcome: 21.8% in the warfarin arm and 22.1% in ASA arm

- **SAMMPRIS:** Stopped early. Increase events in stenting arm.
- DAPT + aggressive risk factor management → recurrence risk 5.5% at 30 days, 12.2% at 1 year and 17.2% at 2 years

- **TOSS-2:** Clopidogrel + ASA vs Cilostazol +ASA (4.4% vs 6.5% at 7 /12)

Background and Rationale

- CHANCE ICAD sub group analysis: ICAD (n=608) had higher rates of recurrent stroke (12.5% vs 5.4%; p=0.0001) at 90 days
- No benefit of DAPT on the primary outcome of stroke (0.79 [0.47–1.32] vs 1.12 [0.56–2.25]; interaction p 5 0.522)
- American Heart / American Stroke Association guidelines do not recommend use of DAPT for prevention of recurrent stroke in ICAD
- Canadian guidelines still recommend DAPT for 90 days

Background and Rationale

- COMPASS trial: rivaroxaban 2.5mg twice daily plus ASA vs rivaroxaban 5mg twice daily vs ASA 100mg in 27,395 patients
- 49% reduction of ischemic stroke (0.51 (0.38–0.68) <0.001)
- Prior ischemic stroke → 77% reduction, no increase in ICH ((Sharma et al, Circulation 2018)
- Major hemorrhage rate (according the modified ISTH criteria) was higher in the combination arm (no increase in hemorrhagic stroke or fatal hemorrhage)

Possible explanation

- ? preventing strokes due to emboli arising from non- stenotic atherosclerotic plaques

JAMA Neurology | Original Investigation

Association Between Low-Dose Rivaroxaban With or Without Aspirin and Ischemic Stroke Subtypes
A Secondary Analysis of the COMPASS Trial

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There were significantly fewer cardioembolic strokes (hazard ratio [HR], 0.40 [95% CI, 0.20-0.78]; *P* = .005) and embolic strokes of undetermined source (HR, 0.30 [95% CI, 0.12-0.74]; *P* = .006)

NEJM journal watch neurology

COMMENT

The number of strokes in each of the subtype categories is fairly low. However, low-dose rivaroxaban plus aspirin seems to have potential benefit in patients predisposed to embolic or ESUS strokes. Although this strategy is not recommended in guidelines yet, low-dose R+A could be an option for patients who cannot tolerate full-dose anticoagulation or patients with recurrent events on antiplatelet therapy alone.

CATIS-ICAD Study Design

Objectives

- Establish safety and efficacy of combination antithrombotic therapy in preventing recurrent ischemic stroke and covert brain infarcts in patients with ICAD

1. To determine the feasibility of recruitment that would support a phase III study

2. To acquire safety data about combination antithrombotic therapy in this specific patient population

Hypotheses

- Feasibility:
  - Feasible to recruit ~ 5 patients per site per year with minimal loss to follow up

- Safety:
  - There will be no clinically-important increase in intracranial hemorrhage with rivaroxaban plus ASA compared with antiplatelet therapy

- Efficacy:
  - Treatment with low-dose rivaroxaban plus ASA will reduce the risk of recurrent ischemic stroke and incident covert brain infarcts detected by magnetic resonance imaging (MRI) at study entry and repeated at end-study

Key Inclusion Criteria

1. Age ≥ 40 years

2. Recent brain ischemia attributed to ICAD of 30-99% as evidenced by CT or MR angiography, occurring between 7 to 100 days prior to randomization and consisting of either:

a. a high-risk TIA defined as; TIA with motor and/or speech involvement

or

b. an ischemic stroke

Key Exclusion Criteria

1. Indication for long-term dual antiplatelet or anticoagulant therapy (e.g venous thromboembolism, coronary stent, mechanical prosthetic valve)
2. Intracranial arterial occlusion (e.g. 100% stenosis) responsible for the acute brain ischemia
3. Intracranial arterial stenosis secondary to causes other than atherosclerosis
4. Extracranial carotid artery stenosis ipsilateral to the qualifying brain ischemia with plans for carotid revascularization
5. Intraluminal thrombus
6. Atrial fibrillation or a history of atrial fibrillation
7. Subdural hematoma in the previous 12 months
8. Previous spontaneous hemorrhagic stroke (eg. intracerebral or subarachnoid hemorrhage)
9. Modified Rankin Scale (mRS) ≥ 4 at entry

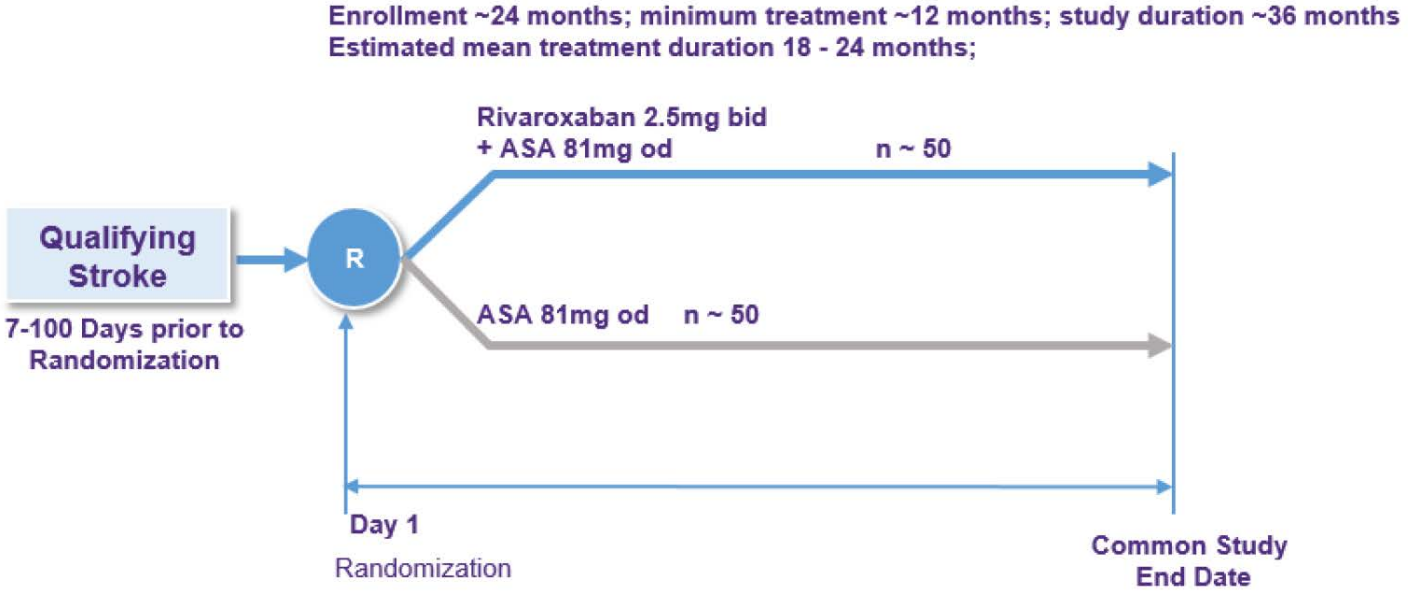
Outcomes - Primary

- The primary feasibility outcome is recruitment rate, refusal rates and retention rates
- The primary safety outcome is intracranial hemorrhage
- The primary clinical efficacy parameter is all recurrent ischemic stroke and MRI-detected incident brain infarctions assessed by MRI at study entry and end-study

Outcomes - Secondary

- Major hemorrhage defined by ISTH criteria
- Combination of ISTH major hemorrhages and clinically-relevant non-major hemorrhages
- Incident MRI-detected covert brain infarctions
- Recurrent ischemic stroke restricted to the territory of the qualifying stenosis
- Stroke, MI, or vascular death
- All-cause mortality

Schematic


Enrollment ~24 months; minimum treatment ~12 months; study duration ~36 months
Estimated mean treatment duration 18 - 24 months;
Rivaroxaban 2.5mg bid
+ ASA 81mg od
n ~ 50
Qualifying Stroke
R
ASA 81mg od
n ~ 50
7-100 Days prior to Randomization
Day 1
Randomization
Common Study End Date

Schedule of Activities

Procedure	Screening (up to 100 days before Rand)	Study Visits									EOT	Notes E/D = Early Discontinuation
		Rand	1M (day 25-40)	3M) (±14 days)	6M (±14 days)	12M (±14 days)	18M (±14 days)	24M (±14 days)	30M (±14 days)	36M (±14 days)		
		Clinic	Clinic	Tel	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	
Informed consent	X											
Inclusion and exclusion criteria	X											
Demographics	X											
Physical examination	X											
Medical history	X											
Current medications	X											
MRI	X										X	
NIHSS		X			X	X	X	X	X	X	X	
mRS		X			X	X	X	X	X	X	X	
SAGE		X				X					X	
Drug Dispensation & accountability		X			X	X	X	X				
Blood Pressure Monitoring		X	X		X	X	X	X	X	X	X	
Study Outcome Events, AE/SAE review		X	←==========→								X	
Concomitant medication		X	←==========→								X	