Comparison of Anti-coagulation vs ant-Platelet Therapies for Intracranial Vascular Atherostenosis

Brian Hoh (UF)
Marc Chimowitz (MUSC)
Sharon Yeatts (MUSC)
Larisa Cavallari (UF)
Symptomatic ICAD

- sICAD: one of most common causes of stroke worldwide\(^1\)
- 8-10% of strokes in the US\(^2\) (~80,000 per year)
- SAMMPRIS: randomized 451 sICAD patients to stenting vs medical management\(^3\)
  - 27% one-year symptomatic infarct or death in medical arm subjects who qualified by symptomatic infarct\(^4\)
- Clearly there is a need for better treatment

2. Sacco et al, Stroke 1997
3. Chimowitz et al, NEJM 2011
4. Lynn & Chimowitz, personal communication
Dual Antiplatelet for sICAD

- Aspirin + clopidogrel default standard after SAMMPRIS
- In post-SAMMPRIS survey of US neurologists, 5%, 45%, and 44% indicated they treat sICAD with clopidogrel + aspirin for 30 days, 90 days, and indefinitely, respectively\(^1\)
- In CAPTIVA StrokeNet feasibility survey (159 sites responded, 2017): 93% clopidogrel + aspirin, 4% aspirin alone, 2% provider judgement, 1% clopidogrel or aspirin

1. Turan et al, Cerebrov Dis 2014
Anticoagulation for sICAD

• WASID failed to show benefit of warfarin vs aspirin for 50-99% sICAD (21.8% vs 22.1% ischemic stroke, brain hemorrhage or vascular death)\(^1\)

• However on post-hoc analysis, if INR 2-3\(^1\)
  • Ischemic stroke 5.1% vs 24.9% if INR <2
  • Major hemorrhage 3.5%

• Suggests when properly dosed, anticoagulation could be effective in preventing ischemic stroke from sICAD

1. Chimowitz et al, NEJM 2005
NOACs

• Novel oral anticoagulants (NOACs): direct thrombin and Xa inhibitors

• COMPASS: 27,395 CAD/PAD subjects randomized to low dose rivaroxaban+aspirin vs rivaroxaban vs aspirin

  • Low dose rivaroxaban+aspirin had fewer primary endpoint (CV death, stroke, MI) than aspirin: 4.1% versus 5.4% (HR 0.76, 95% CI 0.66-0.86, P<0.001)

  • Fewer ischemic stroke: 0.7% vs. 1.4% (HR 0.51, 95% CI 0.38-0.68, P<0.001)

1. Eikelboom et al, NEJM 2017
NOACs for sICAD

- WASID post-hoc analysis and COMPASS results support a trial evaluating low dose rivaroxaban + aspirin as an alternative treatment to dual antiplatelet therapy for sICAD
- NEJM Editorial accompanying the publication of COMPASS:
- Dr. Eugene Braunwald: “a head-to-head comparison between the addition to aspirin of a second antiplatelet drug versus a very low dose of a factor Xa inhibitor” is needed.

1. Eikelboom et al, NEJM 2017
2. Braunwald, NEJM 2017
CAPTIVA: Aims

• **Primary Aim**: To determine the efficacy of low dose rivaroxaban (2.5mg BID) + aspirin (81mg QD) compared to best dual antiplatelet therapy in preventing one-year symptomatic cerebral infarct or death in patients with symptomatic 70-99% intracranial stenosis
Rivaroxaban (Xarelto)

- Direct factor Xa inhibitor
- FDA approved for prophylaxis of DVT in adults undergoing hip and knee replacement
- FDA approved for stroke prevention for non-valvular atrial fibrillation
  - Rocket AF Trial:\textsuperscript{1} rivaroxaban noninferior to warfarin for preventing stroke with non-valvular atrial fibrillation
  - Significant reduction in ICH and fatal bleeding

1. Patel et al, NEJM 2011
CAPTIVA Design

- Phase 3 prospective multicenter double-blinded randomized controlled trial
- NIH StrokeNET
- 4-year subject recruitment period with 12 month followup
CAPTIVA Design: Subjects

- **Subjects**: Age $\geq 30$, non-severe symptomatic infarct within 30 days of enrollment attributable to 70-99% stenosis of major intracranial artery (ICA, M1, vertebral artery, basilar artery)
  - Non-severe: mRS $\leq 3$
  - Without significant aphasia
  - Symptomatic infarct: AHA/ASA definition, includes CITS
  - % stenosis by CTA or MRA
CAPTIVA Design: Treatment Arms

• All subjects will receive intensive medical management (INTERVENT, SBP<140, LDL<70, antihypertensive, atorvastatin)

• Subjects will be randomized to:
  • low dose rivaroxaban (2.5mg BID) + aspirin (81mg QD) for one year
  • Or best dual antiplatelet therapy for one year

• Subjects will undergo CYP2C19 genotype testing
CAPTIVA Design: Best Dual Antiplatelet Therapy

• Best dual antiplatelet therapy will be defined by CYP2C19 LOF allele carrier status

• Non-carriers: clopidogrel (75mg QD) + aspirin (81mg QD)

• Carriers: ticagrelor (180mg on day 1, 90mg BID thereafter) + aspirin (81mg QD)
CAPTIVA Design: Genotyping

- Enrolled subjects will have blood (or saliva) sample sent to UF Center for Pharmacogenomics
- Samples genotyped for CYP2C19 *2, *3, *8, *17 (also have capability to test for *4, *5, *6)
- Total turnaround time <72 hours (in meantime, patients treated with aspirin+clopidogrel)
CYP2C19

- Clopidogrel: pro-drug, requires cytochrome P450 2C19 (CYP2C19) enzymatic activation
- 30% population carriers CYP2C19 single nucleotide LOF polymorphism (*2, *3) (*8 is also LOF) and thus have reduced clopidogrel efficacy
- Multiple meta-analyses of ACS/PCI patients: LOF carriers significantly increased risk of cardiovascular death, MI, stroke, or stent thrombosis\(^1\text{-}^6\)

1. Dahabreh et al, AHRQ 2013
2. Sofi et al, Pharmacogen 2011
3. Mega et al, JAMA 2010
### CYP2C19: Stroke

- **CHANCE**: 2933 patients with *CYP2C19* genotyping

<table>
<thead>
<tr>
<th></th>
<th>LOF Non-Carriers</th>
<th>LOF Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day recurrent stroke</td>
<td>6.7% aspirin+clopidogrel 12.4% aspirin</td>
<td>9.4% aspirin+clopidogrel 10.8% aspirin</td>
</tr>
<tr>
<td></td>
<td>P=0.02</td>
<td>P=NS</td>
</tr>
<tr>
<td>Secondary composite</td>
<td>6.7% aspirin+clopidogrel 12.5% aspirin</td>
<td>9.4% aspirin+clopidogrel 10.9% aspirin</td>
</tr>
<tr>
<td>endpoint (ischemic stroke</td>
<td>P=0.02</td>
<td>P=NS</td>
</tr>
<tr>
<td>hemorrhagic stroke,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>vascular death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90-day recurrent stroke</td>
<td>5.3% aspirin+clopidogrel 7.9% aspirin</td>
<td>6.6% aspirin+clopidogrel 6.3% aspirin</td>
</tr>
<tr>
<td>in subjects w/large artery atherosclerosis</td>
<td>P=0.04</td>
<td>P=NS</td>
</tr>
</tbody>
</table>

1. Wang et al, JAMA 2016
CYP2C19-Guided Therapy

- Prospective multicenter study of 1815 PCI patients (IGNITE)\(^1\)
- LOF carriers treated with CYP2C19-guided antiplatelet therapy (switch to prasugrel, ticagrelor, or triple-dose clopidogrel)
  - Risk of major adverse cardiovascular events (MACE) similar to non-carriers treated with clopidogrel
  - CYP2C19-LOF carriers treated with clopidogrel have significantly higher risk of MACE within 12 months than LOF carriers treated with alternative therapy (prasugrel, ticagrelor, or triple-dose clopidogrel): 23.4 vs. 8.7 per 100 patient-years (HR 2.26; 95% CI 1.18-4.32, \(P=0.013\)).

\(^1\) Cavallari et al, JACC Cardiov Interv 2018
Ticagrelor (Brilinta)

- P2Y12 inhibitor, new class of drug cyclopentyl-triazolo-pyrimidine (clopidogrel, prasugrel, ticlopidine are thienopyridines)
- Not a pro-drug, does not require hepatic CYP2C19 activation
CAPTIVA Design: Endpoints

**Primary:** any symptomatic infarct (AHA/ASA definition, includes CITS) or death within 12 months

**Secondary:**
- Disabling cerebral infarct from enrollment to 12 months
- Any vascular death from enrollment to 12 months
- Myocardial infarction from enrollment to 12 months
- Functional outcome at 12 months as measured by the Rankin Scale and Barthel Index
- Cognitive outcome at 90 days and 1 year as measured by the Montreal Cognitive Assessment (MoCA)

**Safety Endpoints:** Any major bleeding (PLATO definition) from enrollment to 12 months
CAPTIVA Sample Size

- Two-sample survival analysis comparing time-to-event of two randomized treatment arms
- Medical arm of SAMMPRIS: 27% one-year symptomatic infarct or death in subjects who qualified by stroke\(^1\)
- CTA or MRA may overestimate stenosis, so assume lower event rate 24% (11% relative risk reduction to SAMMPRIS)
- Furthermore, assume even lower event rate in the best dual antiplatelet arm of 21% in the current trial (12% relative reduction compared to 24%, 22% relative reduction compared to SAMMPRIS) because
  - CYP2C19 LOF carriers who are randomized to dual antiplatelet therapy will be treated with ticagrelor rather than clopidogrel
  - All subjects in the study will receive 12 months of dual antithrombotic therapy rather than 90 days which they received in SAMMPRIS.
CAPTIVA Sample Size

- **Considerations:**
  - Reduction in the rate of symptomatic infarct and death that would be required to overcome the higher cost of rivaroxaban and aspirin (versus the cost of genotyping subjects and using best dual antiplatelet treatment)
  - Anticipated higher risk of major hemorrhage in the rivaroxaban arm
  - COMPASS trial demonstrated a 50% relative risk reduction in ischemic stroke in the low dose rivaroxaban + aspirin arm compared to aspirin alone
  - This benefit may have been less if dual antiplatelet treatment had been used in the control arm.
  - Thus 30% relative risk reduction is clinically relevant
CAPTIVA Sample Size

- To detect 30% risk reduction with 80% power, using a two-sided 0.05 level of significance, and assuming 10% drop-out, and after inflation for two interim analysis for both efficacy and futility, conducted at 33% and 67% of the enrolled sample according to an O’Brien-Fleming error spending function, the final sample size is

- 1277 subjects

1. Lynn & Chimowitz, personal communication
2. Turan et al, Cerebrov Dis 2014
3. Wang et al, presented at ISC Feb 2017
CAPTIVA Statistical Methods

- All subjects followed for 12 months for primary outcome of any symptomatic infarct or death and analyzed according to intention-to-treat
- Time elapsed between randomization and event occurrence will be calculated
- Subjects who do not experience the event within the 12-month follow-up period will be censored at 12 months
- Subjects who are lost-to-follow-up or withdraw consent will be censored at the time of last patient contact
- The treatment arms will be compared via Cox proportional hazards model, adjusting for older age and infarct in the territory of the stenotic artery prior to the qualifying stroke
CAPTIVA Rationale for 12 month treatment arms

- SAMMPRIS: while event rate highest in first 30 days, there continued to be events beyond 30 days to the 12-month timepoint after which events plateaued\(^1\)

- Currently no data to support 90 day vs >90 day treatment for sICAD

- COMPASS: treatment was long-term\(^2\)

1. Chimowitz et al, NEJM 2011
2. Eikelboom et al, NEJM 2017
Comparison of Anti-coagulation vs anti-Platelet Therapies for Intracranial Vascular Atherostenosis

Thank You