Issues with Antithrombotic Agents in Acute Stroke

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Disclosures

- No commercial interests
- No conflicts of interest

Antiplatelet Issues

- Dual vs single antiplatelet therapy
- Aspirin failure

Anticoagulation Issues

- Anticoagulation options
- When to anticoagulate after ischemic stroke?
- When to anticoagulate after hemorrhagic stroke?

Antiplatelet Agents: Is more better, or worse?

MATCH

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial

*Hans-Christoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu, Hans-Jürgen Rupprecht, on behalf of the MATCH investigators**

Lancet 2004; 364: 331–37

See Comment page 305

- Lancet 2004; 364: 331-37

- MATCH
  - Clopidogrel + ASA vs Clopidogrel alone
  - 7599 patients, 18 months
  - Primary endpoint: MI, Stroke, Vasc death, Hospitalization for ischemia
    - Clopidogrel alone: 16.7%
    - Clopidogrel + ASA: 15.7%
  - Life-threatening hemorrhage
    - Clopidogrel alone: 1.3%
    - Clopidogrel + ASA: 2.6%

SPS3

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*

- NEJM 2012; 367: 817-25

- SPS3
  - Lacunar infarcts, 3020 patients, 3.4 yrs followup
  - Primary endpoint: Recurrent stroke
    - Clopidogrel + ASA: 2.5% per year
    - ASA alone: 2.7% per year
  - Major hemorrhage
    - Clopidogrel + ASA: 2.1% per year
    - ASA alone: 1.1% per year
  - Increased all-cause mortality in dual a/platlet group (hazard ratio, 1.52; 95% CI, 1.14 to 2.04; P = 0.004)

CHANCE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHAN N Engl J Med 2013;369:11-19.

- NEJM 2013; 369: 11-19

- 5170 patients within 24 hours of TIA/minor stroke
- Primary outcome: ischemic or hemorrhagic stroke at 90 days
  - Clopidogrel + ASA: **8.2%**
  - ASA: **11.7%**
  - Hemorrhage rate: 0.3% in both groups

Problems with CHANCE

- Chinese population only:
- Much lower inhibition of P2Y12 receptor
  - Increased incidence of loss of function allele for CYP2C19
  - Less conversion of clopidogrel to active metabolite which binds to P2Y12 receptor
- Uncontrolled hypertension in over 60%
- Use of traditional herbal remedies with antithrombotic properties in 24%
- 9 out of 10 screened patients were excluded from the trial
- Stroke rate is much higher than in North American centres

Single antiplatelet agent use is reasonable. Dual antiplatelet use in some patients may be safe for up to 90 days after the index event

What about ASA failure?

Is it really “failure”, or in line with the expected risks?

- Out of 1000 acute stroke patients, ASA prevents about 9 vascular events within the first month of acute stroke
  - 8.2% (ASA) vs 9.1% (placebo)

- 36 fewer vascular events over 29 months
  - 21.4% (placebo) vs 17.8% (ASA)

Factors which affect ASA

- Compliance
  - In one NHS study, low-dose ASA was taken only 46.6% of the time over a 2.53 year period
    - Br J Clin Pharm 2004, 57(2):188-198
  - In ESPS/2 and Dutch TIA trial, 8 to 10% noncompliance rate

Factors which affect ASA

- NSAIDs
  - Ibuprofen eliminates ASA antiplatelet effect
- Aspirin resistance?

Does “Aspirin resistance” matter?

- Analysis of NINDS and TOAST trials

Journal of Stroke and Cerebrovascular Diseases, Vol. 22, No. 2 (February), 2013: pp 100-106

- 35 to 40% of enrolled patients were on ASA at the time of stroke
  - Patients remained on ASA after stroke

- **Didn’t make a difference in recurrent stroke in the next year**

No role for dual antiplatelet therapy in lacunar stroke

- In the SPS3 trial, patients who were already on ASA when they had their TIA/stroke did not benefit from addition of clopidogrel

- **ASA + placebo:** **Risk of stroke 3%/year**
- **ASA + Clopidogrel:** **Risk of stroke 2.8%/year**

- Neurology® 2014;82:382–389

What do the CSBPRs say?

- At the present time, there is not enough evidence to guide management if a patient has a stroke while on a specific antiplatelet agent. Some clinicians may choose to switch to an alternate antiplatelet agent. In all cases other vascular risk factors should be aggressively managed [Evidence Level C].

Oral Anticoagulants: So many choices!

Oral Anticoagulants

- Warfarin, Dabigatran, Rivaroxaban, Apixaban

- The choice of anticoagulant should be based on trial evidence and real-world considerations

RE-LY: N Engl J Med 2009;361:1139-51.

- Stroke at 1 year
  - Warfarin: 1.69%
  - Dabigatran 1.53%
  - Dabigatran 150 mg bid: 1.11%
- Major hemorrhage rate:
  - Warfarin: 3.36%/yr
  - Dabigatran 150 mg bid: 3.11%/yr
- Intracranial Hemorrhage:
  - Warfarin: 0.38% per year
  - Dabigatran 150 mg bid: 0.1% per year

Dabigatran in the real world

- If you have a patient with therapeutic INR more than 70% of the time, then dabigatran has higher mortality than warfarin
- More people in the trial tolerated warfarin than dabigatran, due to dyspepsia with the latter
- The hemorrhage rate with warfarin in the trial was much higher than in previous warfarin trials

ROCKET-AF: N Engl J Med 2011; 365:883-89

- Ischemic stroke (ITT):
  - Rivaroxaban 20 mg OD: 1.62%/yr
  - Warfarin: 1.64%/year
- Major bleeding (on treatment):
  - Rivaroxaban: 3.6%/yr
  - Warfarin: 3.45%/yr
- ICH rate:
  - Rivaroxaban: 0.26%/yr
  - Warfarin: 0.44%/yr

Rivaroxaban in the real world

- Warfarin patients in the trial as a group had nontherapeutic INR 48% of the time

- Is this what you see in your practice?

- **This is, in fact, what is seen in most practices in the real world**
  - Dlott JS, George RA, Huang X, et al. National assessment of warfarin anticoagulation therapy for stroke prevention in atrial fibrillation. Circulation. 2014;129:1407-1414.

- But with good patient education and motivated, experienced staff, TTR can be as high as 75%

ARISTOTLE: N Engl J Med 2011;365:981-92.

- Ischemic stroke:
  - Apixaban: 1.27%/yr
  - Warfarin: 1.6%/yr
- Major bleeding:
  - Apixaban: 2.13%/yr
  - Warfarin: 3.09%/yr
- ICH:
  - Apixaban: 0.24%/yr
  - Warfarin: 0.47%/yr

Apixaban in the real world

- No efficacy over warfarin in the 7,000 patients recruited in Europe (18,000 pts in whole trial)
- Be cautious with the trial data:
  - Data quality issues, including **fraud**, in 24/36 Chinese sites
  - Couldn’t demonstrate compliance with meds in the trial

Anticoagulation choice should be based on efficacy from clinical trials *and* on real-world feasibility for your patients

Anticoagulation after ischemic stroke

- About 1 to 2% of patients with atrial fibrillation on NOAC will have stroke

- When to restart anticoagulation after ischemic stroke?
- When to restart anticoagulation after hemorrhagic stroke?

Anticoagulation after Ischemic Stroke

- In a systematic review of 23 748 patients, starting anticoagulation a few days after ischemic stroke reduced the number of recurrent strokes but at a cost of increased hemorrhage

“1-3-6-12 day rule”

- After TIA: start within a day
- After small infarct: 3 days (e.g. less than 2 cm in largest dimension)
- After moderate infarct: 6 days (e.g. ASPECTS 8)
- After large infarct: 12 days (e.g. ASPECTS 7 or less)

Timing of Anticoagulation after Hemorrhagic Stroke

- Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S. Optimal timing of resumption of warfarin after intracranial hemorrhage.
  - *Stroke* 2010; **41:**2860–6.

- Retrospective analysis of 177 patients followed for median of 69 weeks
- Risk of recurrent ICH after restarting warfarin was highest in the first 35 days (0.75% per day)
- Risk of stroke in patients not anticoagulated in first 77 days was 0.068%/day
- Combined risk of recurrent ICH and ischemic stroke was lowest when warfarin restarted between 10-30 weeks

What about Amyloid Angiopathy?

- Risk of recurrent hemorrhage is high when many cerebral microbleeds present:
  - 25-40% recurrent ICH in 4 years
- Mortality of ICH with anticoagulation remains 50-60 %