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Farzin Majeed Dr.
Aga Khan University

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COMMENTARY - NEUROLOGY

For this issue abstracts of three recently published articles related to stroke have been selected. They focus mainly on acute and chronic stroke management. The first is the NIH-funded, randomized trial SAMMPRIS, comparing aggressive medical management alone with medical therapy and stenting. While the optimal treatment paradigm for ICAD is unknown, great interest has been generated in endovascular techniques (angioplasty and stenting) to reduce stroke rates. This study is an excellent example how well a trial can be done, and how important are clinical trials in accessing treatments which appear to have benefits but do not actually improve outcomes for patients.

The outlook of acute stroke treatment remarkably changed with the approval of alteplase and improved with extension of time -window. But, the safety and efficacy of alteplase in routine clinical practice needs to be investigated in each country. This study is a post-marketing analysis for the reassessment of the benefit- to- risk profile of intravenous alteplase treatment in Japanese patients.

Previous trials have shown that adding Clopidogrel to aspirin therapy reduces stroke but increases hemorrhage in patients with atrial fibrillation who are not candidates for warfarin therapy. This article presents post-hoc analysis of active trials to observe quantitative benefit of dual anti-platelet therapy. However, the authors could not exclude the possibility that adding clopidogrel had any benefit or even small harm in these patients.

Dr. Farzin Majeed,
Neurovascular Fellow,
Aga Khan University and Hospital,
Karachi,
Pakistan.

N Engl J Med. 2011 Sep 15;365(11):993-1003.

Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, Hoh BL, Hourihane JM, Levy EI, Alexandrov AV, Harrigan MR, Chiu D, Klucznik RP, Clark JM, McDougall CG, Johnson MD, Pride GL Jr, Torbey MT, Zaidat OO, Rumboldt Z, Cloft HJ; SAMMPRIS Trial Investigators.

Department of Neurosciences, Medical University of South Carolina, Charleston, SC 29425, USA. mchimow@musc.edu

STENTING VERSUS AGGRESSIVE MEDICAL THERAPY FOR INTRACRANIAL ARTERIAL STENOSIS

BACKGROUND: Atherosclerotic intracranial arterial stenosis is an important cause of stroke that is increasingly being treated with percutaneous transluminal angioplasty and stenting (PTAS) to prevent recurrent stroke. However, PTAS has not been compared with medical management in a randomized trial. **METHODS:** We randomly assigned patients who had a recent transient ischemic attack or stroke attributed to stenosis of 70 to 99% of the diameter of a major intracranial artery to aggressive medical management alone or aggressive medical management plus PTAS with the use of the Wingspan stent system. The primary end point was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period or stroke in the territory of the qualifying artery beyond 30 days. **RESULTS:** Enrollment was stopped after 451 patients underwent randomization, because the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8%

in the medical-management group (nonfatal stroke, 5.3%; non-stroke-related death, 0.4%) ($P=0.002$). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Currently, the mean duration of follow-up, which is ongoing, is 11.9 months. The probability of the occurrence of a primary end-point event over time differed significantly between the two treatment groups ($P=0.009$), with 1-year rates of the primary end point of 20.0% in the PTAS group and 12.2% in the medical-management group. **CONCLUSIONS:** In patients with intracranial arterial stenosis, aggressive medical management was superior to PTAS with the use of the Wingspan stent system, both because the risk of early stroke after PTAS was high and because the risk of stroke with aggressive medical therapy alone was lower than expected. (Funded by the National Institute of Neurological Disorders and Stroke and others; SAMMPRIS ClinicalTrials.gov number, NCT00576693.).

Stroke 2010, 41:1984-1989:

Jyoji Nakagawara, MD; Kazuo Minematsu, MD; Yasushi Okada, MD; Norio Tanahashi, MD; Shinji Nagahiro, MD; Etsuro Mori, MD; Yukito Shinohara, MD; Takenori Yamaguchi, MD; for J-MARS Investigators

Nakamura Memorial Hospital, Hokkaido, Japan. george@med.nmh.or.jp

THROMBOLYSIS WITH 0.6 MG/KG INTRAVENOUS ALTEPLASE FOR ACUTE ISCHEMIC STROKE IN ROUTINE CLINICAL PRACTICE. THE JAPAN POST-MARKETING ALTEPLASE REGISTRATION STUDY (J-MARS)

BACKGROUND AND PURPOSE: In Japan, alteplase at 0.6 mg/kg was approved in October 2005 for use within 3 hours of stroke onset by the Ministry of Health, Labor and Welfare (MHLW). The aim of the Japan post-Marketing Alteplase Registration Study

METHODS: A total of 7492 patients from 942 centers were enrolled in the J-MARS, an open-label, nonrandomized, observational study, from October 2005 to October 2007. Primary outcome measures were symptomatic intracranial hemorrhage (a

deterioration in NIHSS score ≥ 4 from baseline) and favorable outcome (modified Rankin Scale score, 0-1) at 3 months after stroke onset.

RESULTS: The proportion of patients with symptomatic intracranial hemorrhage in 7492 patients (safety analysis) was 3.5% (95% confidence interval [CI], 3.1%-3.9%) within 36 hours and 4.4% (95% CI, 3.9%-4.9%) at 3 months. The overall mortality rate was 13.1% (95% CI, 12.4%-13.9%) and the proportion of patients with fatal symptomatic intracranial hemorrhage was 0.9% (95% CI, 0.7%-1.2%). The outcomes

at 3 months were available for 4944 patients and the proportion of favorable outcome (efficacy analysis) was 33.1% (95% CI, 31.8%-34.4%). The subgroup analysis in patients between 18 and 80 years with a baseline NIHSS score < 25 demonstrated that favorable outcome at 3 months was 39.0% (95% CI, 37.4%-40.6%).

CONCLUSIONS: These data suggest that 0.6 mg/kg intravenous alteplase within 3 hours of stroke onset could be safe and effective in routine clinical practice for the Japanese.

Ann Intern Med. 2011 Nov 1;155(9):579-586.

Connolly SJ, Eikelboom JW, Ng J, Hirsh J, Yusuf S, Pogue J, de Caterina R, Hohnloser S, Hart RG; on behalf of the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) Steering Committee and Investigators.

McMaster University, Hamilton, Ontario, Canada; Gabriele d'Annunzio University, Chieti, Italy; and Goethe University, Frankfurt,

NET CLINICAL BENEFIT OF ADDING CLOPIDOGREL TO ASPIRIN THERAPY IN PATIENTS WITH ATRIAL FIBRILLATION FOR WHOM VITAMIN K ANTAGONISTS ARE UNSUITABLE

Background: Adding clopidogrel to aspirin therapy reduces stroke in patients with atrial fibrillation (AF) but increases hemorrhage.

Objective: To quantify the net benefit of adding clopidogrel to aspirin therapy, accounting for differences in clinical significance between ischemic and hemorrhagic events.

Design: Observational cohort study to assign the relative weighting of events and post hoc analysis of randomized trial data to assess net benefit of dual antiplatelet therapy in the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) clinical trials. Setting: Global randomized clinical trial. Patients: 10 041 patients with AF, 7554 of whom were not candidates for warfarin therapy.

Measurements: Ischemic events (ischemic stroke or myocardial infarction) and hemorrhagic events (hemorrhagic stroke or subdural or extracranial bleeding), weighted by the hazard ratio for death (or death or disability) after an event relative to death (or

death or disability) after ischemic stroke. The net clinical benefit of dual antiplatelet therapy in the ACTIVE A trial participants was defined as the sum of weighted event incidence with dual antiplatelet therapy subtracted from the sum of weighted event incidence on control treatment, expressed as ischemic stroke equivalents prevented per 100 patients years.

Results: Adding clopidogrel to aspirin therapy prevented 0.57 ischemic stroke equivalent (95% CI, -0.12 to 1.24) per 100 patient-years of treatment when weighted by hazard for death after ischemia or hemorrhage and 0.67 ischemic stroke equivalent (CI, -0.03 to 1.18) when weighted by death or disability after ischemia or hemorrhage.

Limitation: No attempt was made to relate deaths used for weighting to events; disability data were missing for more than one half of patients.

Conclusion: Adding clopidogrel to aspirin therapy resulted in a modest net benefit among patients with AF for whom warfarin was unsuitable. The benefit

would probably be clinically relevant for some patients, but estimates could not exclude the possibility of either no benefit or very small harm in this population.

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