



## Stroke Treatment: Current News and Developments

### *İnme Tedavisi: Güncel Haber ve Gelişmeler*

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#### Stroke Treatment: Current News and Developments

Several studies regarding the treatment of both acute ischemic and hemorrhagic stroke, and the secondary prevention have been completed and presented in the first few months of this year. The main results of these controversial studies are discussed in this article.

#### **Neurothrombectomy is the new standard in the treatment of acute ischemic stroke.**

During the 9<sup>th</sup> World Stroke Congress in Istanbul, the treatment of acute stroke entirely changed with presentation of the positive results of the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MrClean) study on October 28<sup>th</sup>, 2014, regarding the effectiveness of thrombectomy. Following the announcement of these positive results, data collection in other thrombectomy studies with similar designs was aborted and the results were subjected to analysis; all neurologists became enthusiastic about the positive results for which they had been waiting for (1). However, this enthusiasm has waned after a more careful evaluation of the situation, because many countries, including Turkey, do not have the economic capacity to broadly and ethically implement this treatment. Therefore, it is believed that it is time to reorganize and implement the national acute stroke treatment system (2). The use of previous methods is no longer possible. The results were striking and they cannot be ignored. The highly effective reperfusion evaluated in Multiple Endovascular Stroke collaboration pooled data from five trials and found that the number needed to treat with endovascular thrombectomy to

reduce disability by at least one level on the modified Rankin scale for one patient was 2.6 (3). Of course, this rate is a very rare; a fairly low rate in medicine. However, thrombectomy should be performed within 6-12 hours after stroke, so patients must be referred to eligible treatment centers within this short period of time known as the “therapeutic window.” In this case, regional regulations and national dissemination seems to be obligatory. Stroke can be observed everywhere, not only in metropolises, and every patient with severe stroke can only be treated in this way. Turkey was one of the last countries in Europe to initiate intravenous thrombolytic treatment. To avoid a similar situation in thrombectomy, and for the benefit of our patients and people, this scientific data must be implemented in Turkey with a collaborative and multidisciplinary approach. It is clear that Turkish Neurological Society should undertake the most critical role in this context.

#### **Low-dose intravenous thrombolytic treatment is not more effective in acute ischemic stroke.**

In the Enhanced Control of Hypertension and Thrombolysis Stroke Study, low-dose (0.6 mg/kg) and standard dose (0.9 mg/kg) intravenous tissue plasminogen activator (tPA) were compared in 3.310 patients within 4.5 hours of the onset of stroke (4). The primary outcome was death or disability at 90 days, and was found similar in both groups (53.2% with low-dose tPA and 51.1% with standard dose). However, although mortality rates were less with low-dose, disability rates tended to be higher. This study suggests that 19 patients would not die if 1.000 patients were given low-dose tPA instead of a standard dose, but an extra 40 patients would be disabled. Also, major symptomatic intracerebral hemorrhage was less with low-dose tPA (1% vs. 2.1%). Although

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it is a negative study, these results may be interpreted as “low-dose tPA is safer” by neurologists (5). Therefore, a tendency to administer low-dose tPA in patients at high risk of bleeding could occur automatically. It should be stated that more data are needed to make some practical assumptions without being fascinated by these results (4) and that the power of this study was far from changing the current clinical routine.

#### **There is no effect of therapeutic hypothermia in acute ischemic stroke.**

The results of the ICTuS-2 trial were presented at the International Stroke Conference, which was held in February 2016, in Los Angeles (6). In this study of 120 patients, "endovascular" hypothermia was found to have no benefit either as a combination to thrombolytic treatment or as a stand-alone treatment, and was observed to increase mortality (8.8% with normothermia vs. 15.9% with hypothermia). The increase in mortality was due to the increase in pneumonia in the hypothermia group (19% vs. 10%), and this seems to be an important problem in prevention. The effectiveness of hypothermia in stroke treatment will not be elucidated until the end of the Eurohyp-1 trial in which "external" cooling is being used (7). However, the use of hypothermia in neuro-intensive care units in patients with particularly large infarcts and/or brain edema appears to continue on the basis of the positive results of small studies (8).

#### **Prothrombin complex concentrates are superior to fresh frozen plasma in the correction of defective hemostasis in cerebral bleeding due to warfarin.**

In the International normalized ratio (INR) normalisation in patients with Coumadin-related intracranial Hemorrhages (INCH) trial, prothrombin complex concentrates were found superior to conventional fresh frozen plasma with respect to normalizing INR in patients with intracerebral hemorrhage related to warfarin. Nine percent of patients in the fresh frozen plasma group versus 77% of patients in the prothrombin complex concentrate group reached target INR (1.2 or lower within 3 h of treatment initiation) within the therapeutic window (9). Although the effect of this result on clinical outcomes is still not clear, it is inconceivable that the present INCH data regarding the speed and efficiency of four-factor concentrates will not affect current practice.

#### **Platelet transfusion after intracerebral hemorrhage in people taking antiplatelet therapies does more harm than good.**

One hundred ninety participants with supratentorial intracerebral hemorrhage while on antiplatelet therapy were randomized in the Platelet Transfusion in Cerebral Hemorrhage trial and platelet transfusion within 6 h of symptom onset was shown to increase mortality at 3 months approximately 2-fold (95% confidence interval: 1.18-3.56) (10). Although transfusion of one unit of platelet to 71 patients on acetylsalicylic acid and "two" units of platelet to 16 patients on clopidogrel was non-standard in this study, the increase in hospital complications in the treatment group seems to have made the actual impact on this negative result. Therefore, this still quite common and seemingly reasonable administration (platelet transfusion is performed in about a quarter of antiplatelet therapy-related hemorrhages) should be abandoned until further data.

#### **Effective antidotes have been developed for new oral anticoagulants.**

Long-term, high resolution, and daily monitoring of cardiac rhythm by a variety of methods during the past few years has led to identification of more atrial fibrillation in all patient groups with high vascular risk, including “embolic stroke of unknown cause” (11). The diagnosis and treatment of atrial fibrillation has changed significantly in the last 5 years with the introduction of new oral anticoagulants (NOAC) with less risk of hemorrhage and several prophylactic methods, such as left atrial appendicular closure, during a similar period of time. Of the NOACs, dabigatran, rivaroxaban, and apixaban are available in Turkey. The efficacy of their antidotes, idarucizumab, and andexanet alfa, was also presented recently and this reduces the unwarranted doubts about NOAC. Reliable guidelines on the use of NOACs and antidotes in stroke have been published (12). The effective use of these drugs by neurologists is critical for patients.

#### **Lowering systolic blood pressure in intracerebral hemorrhage in the acute phase does not provide extra benefit.**

Although blood pressure control in the acute phase was shown to be of moderately beneficial in Intensive blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT-2) in 2013, aggressive (rapid and intensive) lowering was presented as having no benefit in the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II) trial in May 2016. A total of 1.000 patients within 4.5 hours of ICH onset, with a hematoma volume less than 60 cm<sup>3</sup> were enrolled in ATACH-II, and the average systolic pressure was lowered to 110 mmHg in the intensive-treatment group, and to 140 mmHg in the standard-treatment group for the duration of 24 hours with intravenous nicardipine. Although intensive blood pressure reduction caused a mild reduction in hematoma expansion, prognosis was not different between the groups (modified Rankin scale score, 4 to 6 at 3 months), rather it remained slightly high (about 1%) in the intensive-treatment group. However, the already achieved effective blood pressure control in 80% of patients prior to randomization in ATACH-II trial might have significantly affected the difference between the treatment groups. However, with the present data and combining the results of the INTERACT-2 and ATACH-II trials, it seems reasonable to keep the systolic blood pressure of patients with acute intracerebral hemorrhage in the range of 120 to 140 mmHg during the first 24 hours.

#### **New standards are needed in carotid artery revascularization.**

The addition of revascularization (stenting or endarterectomy) to medical therapy especially in low-risk groups in cervical carotid artery stenosis continues to be a major topic of discussion (13). Anti-atherosclerotic medical treatment includes meticulous blood pressure, blood glucose, and dyslipidemia treatment and the use of antiplatelet drugs. The most important factor is still about lifestyle modification and includes smoking cessation, adequate physical activity, diet and weight loss. This approach requires the achievement of specific clinical and biochemical targets, and is time-consuming. However, one must keep in mind that neurologists in the ongoing Carotid Revascularization for Primary

Prevention of Stroke-2 trial, in which the effect of revascularization on asymptomatic high-grade carotid stenosis is being investigated, are responsible for achieving monitored targets, including systolic blood pressure and low-density lipoprotein cholesterol. It means that neurologists should follow and treat the vascular diseases of their patients. A striking development in this context was the absence of a difference between stenting and endarterectomy in asymptomatic carotid stenosis (ACT) in the recently published Randomized Trial of Stent versus Surgery for ACT-I (2). Importantly, periprocedural stroke and death risk of below 3%, and 5-year stroke-free survival rate of over 90% indicate the need for revision of the currently accepted thresholds.

### **Ticagrelor is not superior in the prophylaxis of stroke.**

Ticlopidine and clopidogrel, platelet adenosine diphosphate receptor 'P2Y12' antagonists, have been used successfully for many years in the secondary prophylaxis of stroke. Ticagrelor, which is a newer and different member of this group as a nucleoside analog, was compared with aspirin in terms of preventing stroke, heart attack, and death within 3 months after stroke. Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial recruited 13,199 patients with non-cardioembolic stroke or high-risk transient ischemic attack patients from many countries including Turkey. Ticagrelor (a loading dose of 180 mg in the first 24 hours, followed by 90 mg twice daily) demonstrated a similar efficacy like aspirin (a loading dose of 300 mg, followed by 100 mg daily) (14). While ischemic stroke was 5.8% in the ticagrelor group, it was 6.7% in the aspirin group. Ticagrelor caused similar bleeding rates like aspirin. The rates of major bleeding, intracerebral hemorrhage, and fatal bleeding in the ticagrelor and aspirin groups were as follows: 0.5% vs. 0.6%, 0.2% vs. 0.3% and 0.1% vs. 0.1%, respectively. Planned subgroup analysis revealed that ticagrelor would be more effective if used in patients aged less than 65 years with minor (National Institutes of Health stroke score of 3 or less) strokes or strokes during aspirin treatment, within the first 12 hours. But this study was not powerful enough to test these groups and these hypotheses can be considered as subjects for future studies. In clinical practice, switching to classic thienopyridines such as clopidogrel is a common practice in patients with stroke on aspirin. In this context, ticagrelor, which is not a thienopyridine but acts via a similar mechanism, demonstrated supportive data.

### **Ethics**

*Peer-review: Internal peer-reviewed.*

### **References**

1. Bektas H, Cabalar M, Topçuoğlu MA, Arsava EM. Akut İskemik İnmede Endovasküler Tedavi: Son Bir Yılda Ne Değişti? Türk Beyin Damar Hastalıkları Dergisi 2016;22:1-8.
2. Rosenfield K, Matsumura JS, Chaturvedi S, Riles T, Ansel GM, Metzger DC, Wechsler L, Jaff MR, Gray W, Investigators AI. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med 2016;374:1011-1020.
3. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Davalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millan M, Davis SM, Roy D, Thornton J, Roman LS, Ribo M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG, collaborators H. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-1731.
4. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarria VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J, Investigators E, Coordinators. Low-Dose versus Standard-Dose Intravenous Alteplase in Acute Ischemic Stroke. N Engl J Med 2016;374:2313-2323.
5. Sila C. Finding the Right t-PA Dose for Asians with Acute Ischemic Stroke. N Engl J Med 2016;374:2389-2390.
6. Lyden P, Hemmen T, Rapp K, Ernstrom K, Agarwal S, Concha M, Hussain S, Dugan G, Raman R, Grotta J. ICTUS-2 Final Results Program and abstracts of the American Heart Association/American Stroke Association International Stroke Conference 2016; February 17-19, 2016; Los Angeles, California Abstract LB4. 2016 [https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm\\_481852.pdf](https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_481852.pdf) (13-5-2016'da ulasildi) (2016).
7. van der Worp HB, Macleod MR, Bath PM, Demotes J, Durand-Zaleski I, Gebhardt B, Glud C, Kollmar R, Krieger DW, Lees KR, Molina C, Montaner J, Roine RO, Petersson J, Staykov D, Szabo I, Wardlaw JM, Schwab S, Euro HYPi. EuroHYP-1: European multicenter, randomized, phase III clinical trial of therapeutic hypothermia plus best medical treatment vs. best medical treatment alone for acute ischemic stroke. Int J Stroke 2014;9:642-645.
8. Su Y, Fan L, Zhang Y, Zhang Y, Ye H, Gao D, Chen W, Liu G. Improved Neurological Outcome With Mild Hypothermia in Surviving Patients With Massive Cerebral Hemispheric Infarction. Stroke 2016;47:457-463.
9. Steiner T, Poli S, Griebel M, Husing J, Hajda J, Freiberger A, Bendszus M, Bosel J, Christensen H, Dohmen C, Hennerici M, Kollmer J, Stetefeld H, Wartenberg KE, Weimar C, Hacke W, Veltkamp R. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurol 2016;15:566-573.
10. Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB, Investigators P. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet 2016;387:2605-2613.
11. Albers GW, Bernstein RA, Brachmann J, Camm J, Easton JD, Fromm P, Goto S, Granger CB, Hohnloser SH, Hylek E, Jaffer AK, Krieger DW, Passman R, Pines JM, Reed SD, Rothwell PM, Kowey PR. Heart Rhythm Monitoring Strategies for Cryptogenic Stroke: 2015 Diagnostics and Monitoring Stroke Focus Group Report. J Am Heart Assoc 2016;5:e002944.
12. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;17:1467-1507.
13. Chaturvedi S, Sacco RL. Are the Current Risks of Asymptomatic Carotid Stenosis Exaggerated?: Further Evidence Supporting the CREST 2 Trial. JAMA Neurol 2015;72:1233-1234.
14. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS, Committee SS, Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. N Engl J Med 2016;375:35-43.