Another Enchantment From ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study)

Are Savings and Safety More Salutary Than Efficacy?

Peter D. Schellinger, MD; Georgios Tsivgoulis, MD

It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.

—Sir Arthur Ignatius Conan Doyle, 1892, *The Adventures of Sherlock Holmes,* Sherlock Holmes in "A Scandal in Bohemia"

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Ongoing discussions address the optimum dose of r-tPA (recombinant tissue plasminogen activator). Although in most countries in the world, the so-called standard dose of 0.9 mg/kg bodyweight is approved and used (based on numerous randomized controlled trials and joint and meta-analyses), in Japan and some other Asian countries, a low dose of 0.6 mg/kg bodyweight has been proposed or approved. Besides cost issues, the original rationale for the low dose was derived from the fear that Asians are a more bleeding-prone ethnic group and was tested because of safety concerns. On the contrary, the value of having 1 drug at 1 dose for an emergency situation is helpful because it is still a challenge to establish only that worldwide.

After a single-arm nonrandomized study in 103 patients in J-ACT 1[1] (Japan Alteplase Clinical Trial), the dose of 0.6 mg/kg was approved in Japan. Efficacy and safety of this lower-dose thrombolytic therapy were confirmed by postmarketing surveys and registries in Japan, that is, J-ACT 2[2] (58 patients), J-MARS (Japan Postmarketing Alteplase Registration Study[3]; 7492 patients; 4944 with 3-month outcomes), and SAMURAI (Stroke Acute Management With Urgent Risk-Factor, Assessment Improvement Study)[4] (600 patients). All these nonrandomized studies suggested with a low data quality (because of trial design) that intravenous thrombolysis with a 0.6 mg/kg dose achieved numerically similar outcomes and safety end points as comparable data sets from the large randomized controlled clinical trials.

There is nothing like first hand evidence.[5] About 1 year ago, Anderson et al[6] presented and published the results of ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study), a 2-by-2 open-label randomized controlled clinical trials of low- (0.6 mg/kg body weight) versus standard-dose r-tPA in >3300 acute ischemic stroke patients. Despite all following criticism, one needs to bear in mind that the ENCHANTED trial is indeed a large academic clinical trial, which cannot and does not claim to introduce a change to clinical practice but is hypothesis generating. The ENCHANTED trial investigators need to be commended for this genuine effort and their accomplishments. In brief, the trial failed to meet the primary objective in a noninferiority approach with the primary outcome (death or disability according to modified Rankin Scale [mRS] of 2–6) being 2.1% more frequent in the low-dose arm (odds ratio, 1.09; 95% confidence interval, 0.95–1.25; P=0.51 for noninferiority). This main result was not affected by the lower rate of symptomatic intracranial hemorrhages in the low-dose group (1.0% versus 2.1%). Noninferiority and equivalence analyses test whether the new treatment is not unacceptably worse than the old treatment or has a delta close enough to accept equivalence (can there be an unanimous vote on what an adequately small delta is?). Failing to show noninferiority for the low dose of r-tPA establishes the standard dose of r-tPA as what it is: the standard of care! According to the published results of the ENCHANTED trial, rt-PA remains the standard of care for any subgroup that was analyzed, such as blood pressure, baseline stroke severity, history of stroke and diabetes, ethnicity, especially for Asians who comprised almost two thirds of the study population, or patients with or without antiplatelet pretreatment. Although reducing the dose may reduce bleedings, it even more so reduces efficacy. The authors of ENCHANTED trial promote the thought of a low cost and safe alternative to standard treatment. From a safety, or medico-economically speaking saving point of view, a dose reduction of r-tPA seems to be associated with increased rates of death and disability (and the associated cost of especially the latter), because r-tPA dose reduction translates into a decrease of thrombolysis efficacy. Therefore, the ENCHANTED trial with overall well-balanced groups "provided no compelling evidence" for the use of low-dose r-tPA in any ethnic or medical subgroup.[7] This has been extensively discussed in editorials and comments interpreting the ENCHANTED data.[7,8]

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The authors now present the complete and detailed analysis of low- versus standard-dose alteplase in patients on prior antiplatelet therapy from the ENCHANTED trial in this issue of *Stroke*.[9] Although in the original publication, it was already stated that there was no significant interaction (P=0.054) between alteplase dose and antiplatelet treatment with regard to the primary outcome measure (mRS scores of 2–6),[6] in the current publication, the authors come to the conclusion that low-dose alteplase may improve outcomes in thrombolysis-treated acute ischemic stroke patients on prior antiplatelet therapy. According to the literature, the majority (75% to 80%) of all acute ischemic stroke patients undergoing intravenous thrombolysis is not pretreated with antiplatelets[10,11] consistent with the ENCHANTED trial sample (2560/3285; 78%).[6] Patients pretreated with antiplatelets in the ENCHANTED trial were older, had more severe comorbidities, and worse pretreatment functional status (prestroke mRS score of 0: 68% versus 86%) in comparison with patients not pretreated with antiplatelets, reflecting a substantial imbalance between these subgroups that needs to be adjusted for.

The authors mainly report unadjusted analyses. In these unadjusted analyses, prior antiplatelet therapy was significantly associated with worse outcomes, higher mortality, and higher rates of symptomatic intracranial hemorrhages. These associations did not retain their significance after adjustment for baseline imbalances between the 2 groups with and without antiplatelet pretreatment. Unfortunately, the clinically relevant adjusted analyses are only presented in the online-only Data Supplement in the study by Robinson et al.[9] For instance, the adjusted odds ratio of antiplatelet pretreatment for the primary end point (death and disability) was 1.01 (95% confidence interval, 0.81–1.26; P=0.953; Table III in the online-only Data Supplement in the study by Robinson et al[9]). The same holds true for symptomatic intracranial hemorrhages, which with standard dose r-tPA was only more frequent in an adjusted analysis for the ECASS3 (European Cooperative Acute Stroke Study 3) definition, not for the definitions of ECASS2, NINDS (National Institutes of Neurological Disorders and Stroke), IST-3 (International Stroke Trial), SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study), and neither for clinician-reported or fatal ICH (Table IV in the online-only Data Supplement in the study by Robinson et al[9]). The findings of the ENCHANTED adjusted analyses are in line with a recent meta-analysis that evaluated the safety and efficacy of antiplatelet pretreatment in acute ischemic stroke patients treated with intravenous thrombolysis.[12] The investigators failed to document any independent association between antiplatelet pretreatment and functional outcome or death in confounder-adjusted analyses.[12]

"It is an error to argue in front of your data. You find yourself insensibly twisting them around to fit your theories"[13]: the authors' claims that low-dose alteplase may improve outcomes in thrombolysis-treated acute ischemic stroke patients on prior antiplatelet treatment seem not to be fully supported by the presented data. More specifically, the P values for trend/interaction were not significant in 3 out of 4 unadjusted sensitivity analyses (Table V in the online-only Data Supplement in the study by Robinson et al[9]): death or disability (mRS scores, 2–6), death or severe disability (mRS scores, 3–6), and death (mRS score, 6). The same holds true for various symptomatic intracranial hemorrhages definitions (Table VI in the online-only Data Supplement in the study by Robinson et al[9]). In consequence, the authors' conclusion is based on one significant interaction between antiplatelet pretreatment and r-tPA dose in an unadjusted analysis of mRS shift only (Figure 1 in the study by Robinson et al[9]). However, the authors should have additionally evaluated whether the significance of this interaction persisted after adjustment for potential confounders. Notably, the authors' concerns about the safety and efficacy of standard-dose r-tPA in acute ischemic stroke patients with antiplatelet pretreatment are at odds with a recent analysis from the VISTA (Virtual International Stroke Trial Archive).[14] This analysis documented an independent (P=0.0001) association between standard-dose r-tPA and a higher likelihood of 3-month functional improvement in patients pretreated with a single antiplatelet (adjusted common odds ratio, 1.42; 95% confidence interval, 1.19–1.70).[14] Also, it should be acknowledged that for the majority of patients, who were not on prior antiplatelets, the (unadjusted) rates of good outcomes tended to be better with standard-dose treatment compared with the reduced r-tPA dose. The (unadjusted) decrease in odds ratios of the primary outcome in favor of low dose in antiplatelet pretreated patients and in favor of standard dose in nonpretreated patients were identical (16%), as can be discerned in in the study by Robinson et al[9] (Figure 1 and Table V in the online-only Data Supplement). The rates of mRS scores 0 to 1 were also in favor of the standard dose in the subgroup of patients without antiplatelets (51.5% versus 47.7%).

Interpretation of these results is difficult and impaired by factors and limitations also conceded by the authors themselves. Such factors include that ENCHANTED trial is an academic investigator-initiated trial and neither did nor could have the rigorous monitoring and data validation applied in high-end randomized controlled clinical trials being necessary to account for pretreatment details. The variable "prior antiplatelet use" is not equivalent to "the patient was on antiplatelet therapy at the time point of the acute stroke". Therefore, the authors state that ENCHANTED trial is unable to provide any information about the relation of type, dose, combination, duration, indication, and timing of the last dose of antiplatelet therapy before thrombolysis to adverse outcomes—a fact not sufficiently reflected by the authors' conclusion. Again, this is backed only by 1 unadjusted subgroup analysis, that is, low-dose versus standard-dose r-tPA in patients pretreated with antiplatelets showing greater functional improvement (shift in mRS scores) at 3 months. It is, of course, a trifle, but there is nothing so important as trifles.[15] Whether this single unadjusted analysis is a trifle that justifies the call for a randomized controlled trial testing whether a strategy of low-dose intravenous thrombolysis with r-tPA in acute ischemic stroke patients on antiplatelet therapy is not only safer and cost saving but also results in improved functional outcomes remain to be seen. Until then, intravenous thrombolysis at a dose of 0.9 mg/kg of body weight remains the standard of care for all acute ischemic stroke patients independent of their ethnic origin or antiplatelet pretreatment status. This is a fact, not a theory!

If you torture the data long enough, it will confess.

—Ronald H. Coase, 1991 Nobel Prize in Economic Sciences (originally from a speech given at University of Virginia in the 1960s: *If you torture the data enough, nature will always confess)*

Disclosures

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