

ECASS 3 Gets a Warm Welcome From the Stroke Community

Susan Jeffrey

October 2, 2008 (Vienna, Austria) — Results of the third European Cooperative Acute Stroke Study (ECASS 3) were met with prolonged applause and general enthusiasm from stroke experts here at the 6th World Stroke Congress. The findings are expected by many to change the treatment of acute ischemic stroke, providing reassurance even for skeptics that treating patients with tissue plasminogen activator (tPA) up to 4.5 hours is safe and effective.



From left, Dr. Werner Hacke, Dr. Vladimir Hachinski, and Dr. Michael Brainin at the 6th World Stroke Congress.

The trial compared treatment with tPA in the 3-to-4.5-hour window after a stroke with no treatment. To date, tPA is approved for use only up to 3 hours after the onset of symptoms. Results showed treatment in the extended window can still provide "modest but significant" benefit to patients, investigators reported. Although symptomatic intracerebral hemorrhage was higher in treated patients, the rate was not higher than reported previously among patients treated within the currently approved 3-hour window and was not associated with increased mortality.

Werner Hacke, MD, from the University of Heidelberg, in Germany, principal

investigator of the ECASS 3 trial, presented the findings here on behalf of the trialists. He emphasized that although these findings "open the window" for patients who arrive later than the 3-hour time limit, the goal of therapy still must be to treat as soon as possible, since efficacy begins to decline after only 90 minutes from symptom onset.

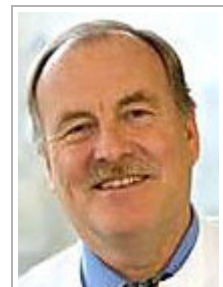
"There may be more time for patients who cannot get in earlier, but there is no more time for physicians," he said. "They have to speed up even more."

The findings were published in the September 25 issue of the *New England Journal of Medicine* and were presented here the same day, although the embargo was lifted by the *Journal* the evening before. The study was supported by Boehringer Ingelheim.

During a press conference, Dr. Hacke said the new results will be considered in the next 6-month review of the European stroke guidelines in November and that it is "highly likely" that the sponsor will apply for regulatory approval of the additional indication.

A "Tremendous Advance"

At the meeting here, *Medscape Neurology & Neurosurgery* polled stroke experts on how they view the ECASS 3 results.



Dr. Werner Hacke
(Source:
University of
Heidelberg)



Dr. Vladimir Hachinski
(Source:
University of
Western Ontario)

These findings represent a "tremendous advance," said Vladimir Hachinski, MD, professor of neurology at the University of Western Ontario, in London, and editor-in-chief of the American Heart Association journal *Stroke*. "It tells us that not only do we have the 3 hours, but we can go beyond, and I think because we have a second study that thrombolysis works, this will convince a number of skeptics that it's a good drug."

I think it's a tremendous advance, because it tells us that not only do we have the 3 hours, but we can go beyond.

At the same time, though, he noted that people should remember another good "treatment" for stroke, organized stroke units, that help patients of all ages and types, whether they are candidates for thrombolysis or not. "I'm not talking about 1 or the other; I'm talking about doing the simple things and then adding this now-extended time window of opportunity to make a difference in stroke," Dr. Hachinski said. "It is so disabling a disease that even a small difference in the outcome of patients makes a big difference in the long term, so I think this is terrific."

Still, Dr. Hachinski said he sees a "big educational challenge" in getting doctors, especially those in specialties other than neurology, to use the drug, because they are frankly "terrified."

"Let's be fair. It's a powerful drug and has powerful side effects," he said. "It's a balance of good vs potential side effects. I think the balance is clearly in favor of doing it, but obviously each case has to be treated individually, and I think there's a risk there. But the risk of not giving it is greater than the risk of giving it, on balance."

Philip Gorelick, MD, John S. Garvin Professor and head of the department of neurology and rehabilitation at the University of Illinois College of Medicine at Chicago and recent chair of the American Heart Association International Stroke Conference, said Dr. Hacke and colleagues are to be congratulated on completing a complex and large-scale trial. "The study has generated good news for stroke patients and for vascular neurologists and other physicians who treat acute ischemic stroke patients, and it will likely influence future acute ischemic stroke treatment guidelines, although in patients with less severe stroke deficits in the extended time window," Dr. Gorelick told *Medscape Neurology & Neurosurgery*.



Dr. Philip Gorelick
(Source:
University of
Illinois College of
Medicine)

A key to using the treatment in this setting will be to minimize hemorrhagic risk, he noted. "It will be interesting to learn of exploratory data from the study regarding predictors of hemorrhage and furthermore to understand information about the distribution of stroke subtypes in the study and response to treatment by stroke subtype," Dr. Gorelick added. "These additional sources of information may help practicing clinicians better apply alteplase in the extended time window, if approved for this indication by major regulatory bodies."

The current study with a 3-to-4.5-hour time window should not be taken as a prescription to delay treatment.

Perfusion/diffusion magnetic resonance imaging (MRI) may play a future role in selecting which patients can be treated in the 3-to-4.5-hour window or even up to 6 hours, he added, based on exploratory findings from the previously published Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and other studies.

Early treatment, however, remains the goal, he emphasized. "The current study with a 3-to-4.5-hour window should not be taken as a prescription to delay treatment of acute ischemic stroke if intravenous [IV] thrombolytic therapy can be administered sooner."

More Patients Treated in 3-Hour Window?



Dr Ralph Sacco
(Source: Miller
School of
Medicine)

Ralph Sacco, MD, from the Miller School of Medicine at the University of Miami, in Florida, called the data "impressive" but said a change in practice should await, first, review of the findings by the American Heart Association/American Stroke Association guidelines committee and, second, approval of the new indication by the Food and Drug Administration (FDA), if the company chooses to seek it.

Faster treatment is better, of course, he said, but this information will provide some flexibility. "It used to be if somebody came in at, say, 2 hours and 20 minutes, it was tough to get everything done and get them treated in within 3 hours," Dr. Sacco told *Medscape Neurology & Neurosurgery*. "Now, if somebody comes in within 3 hours, I think it will be very reasonable to get them treated, should the guidelines change, and should the FDA approve it, within 4.5 hours.

"I think it's exciting for stroke, it's hopeful for the many stroke patients we treat, and it's uplifting to get another positive trial," he said.

But Will Patients Be Treated Later?

Joseph Broderick, MD, from the University of Cincinnati, in Ohio, and a primary investigator of the National Institute of Neurological Disorders and Stroke (NINDS) trial that first established efficacy of tPA in stroke, told *Medscape Neurology & Neurosurgery* that, in his view, the ECASS 3 results are the most important to the field of stroke treatment since the NINDS results were published some 13 years ago.

However, like the ECASS 3 researchers and others, he too is concerned that physicians will take more time if they think they have it. "Unfortunately with physicians, sometimes the more time you have, the more you kind of drag your feet or you want to do another test, and what I worry about is that people will be treated later when it's clear that this is a very time-dependent therapy."



Dr. Joseph Broderick,
(Source:
University of
Cincinnati)

What I worry about is that people will be treated later, and it's clear that this is a very time-dependent therapy.

He said the efficacy in ECASS 3 was similar to that seen in the NINDS trial, although he noted that the ECASS 3 population was a much less severely affected group. "I think their median [National Institutes of Health Stroke Scale] NIHSS score was 9 to 10 as opposed to 14 in the NINDS trial, which is a big difference," he said. "That's why their mortality is extraordinarily low, around 8%, whereas in the [NINDS] trial, the mortality with placebo was 21% and with tPA it was 17%, so you're talking about half the mortality rate, but that reflects the lesser severity of the strokes."

The findings, then, do not provide information on the patients excluded from the trial, Dr. Broderick said. Still, he added, "It's just a great event that builds upon the positive momentum. I still think reperfusion is what it's all about, but reperfusion within a certain time window."

During his presentation, Dr. Hacke acknowledged this limitation for the generalizability of their results but pointed out that the inclusion criteria for the ECASS 3 study were identical to the labeling of tPA for Europe, except for the time window. "So we were not responsible as the investigators that the age limit ended at 80.

We were also not responsible that there was exclusion of patients who had had a prior stroke and were diabetic, but that's what we had to do."



Dr. Mark Alberts

(Source:
Northwestern
Medical Faculty
Foundation)

Mark Alberts, MD, from Northwestern University Medical School, in Chicago, Illinois, said he feels that 1 of the "main victories" of ECASS 3 is the expansion of the time window for IV tPA, making more patients eligible for this therapy. "It also confirms the effectiveness and safety of IV tPA, which has been questioned by a vocal minority of emergency department physicians," he said.

"What I think the challenge is going to be, when and if we rewrite the acute stroke guidelines, is what are we going to say about ECASS 3?" Dr. Alberts said, referring to this difference in populations between the NINDS and ECASS 3 trials. "Are we just going to change the time window for IV tPA to 4.5 hours or make it 1 set of guidelines for patients within 3 hours and another set of guidelines for patients between 3 and 4.5 hours?"

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Dr. Broderick raised essentially this same question to Dr. Hacke during the session, pointing out that the NINDS trial did show a benefit among these older patients with more severe strokes, but only out to 3 hours. Dr. Hacke responded that in clinical practice, doctors have to make decisions based on individual cases but said that he feels that any change to evidence-based guidelines for the 3-to-4.5-hour window would have to reflect the boundaries of the ECASS 3 trial, including the upper age and stroke-severity limits. "In the text, we should be able expound on that, and that finally would be an individual decision to be discussed with the patient and the relatives," he added.

Implications for Ongoing Trials?

Finally, Dr. Broderick pointed out that these findings are going to affect a lot of ongoing trials that are scrambling right now to evaluate what the implications are. "Think about all the trials that are ongoing right now that sort of cede the 3-hour window, saying up to 3 hours we have tPA but after 3 hours, we're using imaging to decide whether or not we should select patients, we're doing device studies," he told *Medscape Neurology & Neurosurgery*. "Well, all of a sudden, we're going to have an effective treatment that's now maybe going out to 4.5 hours, so all those trials are going to have to reconsider."

Dr. Broderick is directing the Interventional Management of Stroke (IMS) 3 trial, for example, an NIH-funded study looking at IV tPA full dose vs two-thirds of the dose followed by endovascular therapy, with 200 patients already randomized. "But we've got a 3-hour time window. Does that mean now that we have to go to 4.5 because the tPA treatment window is going to be moved out? We're going to have to think very hard about that, because it changes our study design, and maybe the effect we expect to see."

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Asked about this latter point, Dr. Hacke told *Medscape Neurology & Neurosurgery* that he had already been approached by a number of investigators with this concern. However, he noted, "until the change in labeling has occurred, there is no legal necessity to do it. We know for sure it works, but it will still be off label until the FDA and the [European Medicines Agency] EMEA and other worldwide institutions have approved the prolonged window. Therefore, any trial that is going on right now can continue, even if they start at 3 hours," he said.

Most centers that participate in clinical trials are highly experienced and will in most countries take the initiative to treat off label, he noted, so he expects many will probably stop randomizing these patients, although they won't be compelled to do so until a new indication for the 3-to-4.5-hour window is approved. "But that will be a period of 2 years, as I learned yesterday," Dr. Hacke added. "Two years." During that time in Europe, he said, thousands of patients will not get the benefit of this therapy.

At least, he said, he is hopeful that the data showing efficacy and safety out to 4.5 hours will provide some confidence to those who had been reluctant to use tPA even within the approved 3-hour window.

Continuing Uncertainty

During the discussion period after the presentation, Peter Sandercock, MD, professor of medical neurology at Western General Hospital, in Edinburgh, Scotland, and co-principal investigator of the ongoing International Stroke Trial 3 (IST 3), said that it is acceptable to continue to randomize patients where there is continuing uncertainty.



"As Werner rightfully emphasized, there are a number of people who are excluded even with the ECASS 3 results," Dr. Sandercock told the meeting here. "These are patients over 80, patients with a prior stroke and history of diabetes, and patients with an NIHSS score of more than 25, and these are areas where we now need randomized scientific evidence. The IST 3 data monitoring committee decided on Tuesday night to continue randomizing patients in the trial to gain important information on whether we can extend treatment even further than the ECASS 3 data suggest is important."

Dr. Jim Grotta
(Source:
University of
Texas Medical
School)

Jim Grotta, MD, from the University of Texas Medical School at Houston, pointed out that the ECASS 3 results appear to exactly replicate what was expected from the pooled analysis of previous randomized trials. "One of the beautiful things about how you designed the trial is that it enables us to pool your data with the existing pooled data," he told Dr. Hacke. Some of these continuing questions such as the effect in older patients could perhaps be answered by pooling the data, Dr. Grotta noted, "so I hope the pooling group will get together fast."

Heady Success

At the meeting here, the heady effect of a positive result in a stroke trial — only the second such result with any pharmacologic therapy after the NINDS trial in 1995 — was tangible in the audience.

At the close of Dr. Hacke's presentation and the prolonged spontaneous applause that followed, Stephen Davis, MD, from the Royal Melbourne Hospital at the University of Melbourne, in Victoria, Australia and comoderator of the session, who was not involved in the study, was effusive.



Dr. Patrick Lyden
(Source:
University of
California, San
Diego)

"I want to warmly congratulate you, the steering committees, the other committees, the sponsor, and the investigators of this landmark study, ECASS 3, this highly successful study that I believe will lead to a change in clinical practice and guidelines and allow the extension of the time window to 4.5 hours with tPA, certainly supported by the meta-analysis and safety data from [the Safe Implementation of Thrombolysis in Stroke Monitoring Study] SITS-MOST," Dr. Davis said. "I think this will also increase the number of patients treated within 3 hours — bearing in mind your comments that no time should be wasted — as well as up to 4.5 hours."

Patrick Lyden, MD, from the University of California, San Diego, and an NINDS trial investigator, wrote the editorial that accompanied the publication of the trial results in the *New England Journal of Medicine*. During the discussion, he said he had had more time perhaps than some others to reflect on what the importance of this trial might be. Although there are some issues that Dr. Hacke and others have pointed out, Dr. Lyden acknowledged, "I think it's very important that we not spend time on minor issues and think about the bigger picture. There should be no more doubt in anyone's mind that intravenous thrombolytic therapy is an effective treatment."

"It's time to stop taking patients to places where either there's reluctance or lack of skill or lack of capacity to give the therapy," he concluded, prompting another burst of applause.

Not Everyone Convinced?

Among the final questions was 1 on whether, in places where intra-arterial thrombolysis was available, Dr. Hacke would use that approach first before intravenous tPA after 3 hours. The question underlines a controversial move by some in the community to use interventional treatments preferentially for the treatment of stroke.

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Dr. Hacke is not among these. Until 3 hours after symptom onset, intravenous tPA is the approved treatment, he said. "In my opinion, there is no good reason, unless you identify a very peculiar situation in a given patient, like a basilar artery occlusion or a carotid T occlusion, to use any intra-arterial device in the presence of an established medical treatment, a medical treatment that yields recanalization rates on the order of 40% to 50% and that has controlled outcome data that are far better than the outcome data that come from uncontrolled, and let me frankly say, lousy case series," he replied bluntly.

That will also be true soon out to 4.5 hours, he added. If the patient is not responding and it becomes clear that there is a tight stenosis of the middle cerebral artery, for example, then an individual decision can be made to use additional rescue therapies, he said.

"But I strongly disagree with any notion that there should be a priority for intra-arterial therapy," Dr. Hacke said. He called on the interventional community to undertake clinical trials to prove the efficacy of these therapies. "And I say that as someone who started with interventional therapies while those colleagues were still in school."

At the end of the session, the moderators called for a show of hands on who, given the ECASS 3 data, would treat a patient showing up at 4 hours after symptom onset with thrombolytic therapy. Dr. Davis called the result a "sizable majority," in favor of treatment, but still, it did not include everyone.

"Can we see who would not?" Dr. Hacke quipped. "So we know where not to go."

ECASS 3 was supported by Boehringer Ingelheim. Dr. Hacke reports receiving consulting, advisory board, and lecture fees from Paion, Forest Laboratories, Lundbeck, and Boehringer Ingelheim and grant support from Lundbeck. He is also an uncompensated member of the editorial advisory board for Medscape Neurology & Neurosurgery. Disclosures for other ECASS investigators appear in the paper. Dr. Gorelick reports that he was on the steering committee for the PROFESS trial, sponsored by Boehringer Ingelheim. Dr. Broderick receives study medication from Genentech for the ongoing NIH-funded IMS study. Dr. Sacco reports receiving consulting fees from Boehringer Ingelheim, GlaxoSmithKline, and Sanofi-Aventis and lecture fees from Boehringer Ingelheim. Dr. Alberts reports he has served as a consultant to and/or received grants for research from Boehringer Ingelheim, Genentech, and others. He is a member of the editorial advisory board for Medscape Neurology & Neurosurgery.

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