The Case
A 55-year-old woman presents with aphasia, left gaze deviation, and right-sided hemiplegia of an undetermined onset time. Computed tomography scan of the brain is normal.

The Questions
1. Should the patient be considered for thrombolysis for suspected ischemic stroke and why?
2. If yes, are other tests required to facilitate the decision making? Should informed consent be obtained before initiation of thrombolytic therapy?

The Controversy
Should patients with suspected ischemic stroke of an undetermined onset time and negative head CT scan be considered for thrombolysis?

A Plain Computed Tomography Scan Is Sufficient to Consider Thrombolysis in Patients With Unknown Time of Onset
Andrei V. Alexandrov, MD

Should the Patient Be Considered for Thrombolysis?
Absolutely, yes! This clinical presentation is typical for a severe left middle cerebral artery stroke (unlikely a mimic), computed tomography scan ruled out hemorrhage, and given clinical suspicion of the extent of ischemia, CT findings of normal tissue appearance point to a mismatch favoring a recent time of symptom onset.

Let us further examine why to consider thrombolysis in this particular case. Aphasic patients may be brought with no witness as to when it exactly happened, but the way where they were found or how they appear sometimes strongly suggests that the event is fairly recent and that their premorbid function was good. Time has emerged as a criterion for eligibility for systemic thrombolysis because we tested the timeframes in large patient populations. Individual times to completion of ischemic damage or lingering on the edge of reversibility vary greatly.1 Therefore, I do not hold the unknown time of symptom onset as an absolute no-go in my decision for thrombolysis. Rather, I make it my own challenge to ascertain the time interval when it could likely have happened and to arrive at a decision what could be done as soon as possible in an attempt to reverse the disability.

In this case, there is an undeniably severe disability that, if it persists, will lead to a complete loss of quality of life. Patients at risk of stroke (who were able to speak for themselves) view aphasia and hemiplegia tantamount to or even worse than death as outcome.2,3 I heard confirmation of the above mentioned research at bedside from some of my acute patients suffering a stroke about their take on receiving thrombolysis: “Doc, make me back like I was or let me go!” Patients fear disability.

However, any risks of an aggressive reperfusion and its currently unknown benefits outside established 3- and 4.5-hour timeframes should be weighed against how much this patient will suffer if neurological functions are not restored. If systemic thrombolysis is given, can a symptomatic intracerebral hemorrhage (the most feared complication) make this patient any worse? Is the chance of dying from symptomatic intracerebral hemorrhage greater than dying from infections, pulmonary embolus, or cardiac complications from an untreated stroke with baseline National Institutes of Health Stroke Scale score of >20 points?

One can argue that there is an equipoise whether to treat or not patients with an unknown time of onset. The fact that randomized trials in this setting have not been completed does not mean there is no evidence that thrombolysis works in these patients. A recent analysis of the Virtual International Stroke Trials Archive showed that outcomes were better with systemic tissue-type plasminogen activator (tPA) compared with controls in patients with label contraindications and...
If the time of symptom onset is unknown or when time from last seen normal exceeds timeframes for an established therapy and ongoing clinical trials at my center, I make my initial decision on the basis of a noncontrast head CT alone. Normal brain tissue appearance or Alberta Stroke Program Emergency CT Score >7 correlates with lesser severity of ischemia and its shorter duration. This case represents a clinical-CT mismatch (high National Institutes of Health Stroke Scale score/normal tissue on CT). I will explain my assessments, natural history of an untreated event, as well as largely unknown risks and benefits of the off-label tPA use in this case to obtain written informed consent from a family member or proxy to start intravenous tPA as soon as possible.

If I have to ascertain that time from symptom onset is likely within the established timeframe for systemic tPA to support this decision making, I would obtain urgent MRI and start it with 2 sequences, diffusion-weighted imaging and fluid attenuated inversion recovery. Diffusion-weighted imaging–positive, fluid attenuated inversion recovery–negative tissue appearance would support earlier presentation from symptom onset and such MR-guided treatment with systemic tPA may be safe.

To save time, I would have obtained consent simultaneously with moving the patient to MRI in anticipation of imaging supportive of treatment, and as soon as these 2 sequences are completed with favorable result, I would interrupt scanning and start intravenous tPA to lose as little time as possible.

If this patient meets criteria for an ongoing clinical trial (ie, unknown time of onset in those who woke up with stroke symptoms), I will follow trial-specific imaging protocol (MRI or CT). Enrollment of patients in these and future trials is a priority to provide answers and evidence-based treatment to more stroke patients.

Disclosures
Dr Alexandrov serves as Consultant to Cerevast Therapeutics, Inc.

References
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Stroke. 2013;44:1492-1493; originally published online April 11, 2013;
doi: 10.1161/STROKEAHA.113.000912
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/5/1492

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