Evaluation of Interval Times From Onset to Reperfusion in Patients Undergoing Endovascular Therapy in the Interventional Management of Stroke III Trial

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Background—Meaningful delays occurred in the Interventional Management of Stroke (IMS) III trial. Analysis of the work flow will identify factors contributing to the in-hospital delays.

Methods and Results—In the endovascular arm of the IMS III trial, the following time intervals were calculated: stroke onset to emergency department arrival; emergency department to computed tomography (CT); CT to intravenous tissue plasminogen activator start; intravenous tissue plasminogen activator start to randomization; randomization to groin puncture; groin puncture to thrombus identification; thrombus identification to start of endovascular therapy; and start of endovascular therapy to reperfusion. The effects of enrollment time, CT angiography use, interhospital transfers, and intubation on work flow were evaluated. Delays occurred notably in the time intervals from intravenous tissue plasminogen activator initiation to groin puncture (median 84 minutes) and start of endovascular therapy to reperfusion (median 85 minutes). The CT to groin puncture time was significantly shorter during working hours than after. Times from emergency department to reperfusion and groin puncture to reperfusion decreased over the trial period. Patients with CT angiography had shorter emergency department to reperfusion and onset to reperfusion times. Transfer of patients resulted in a longer onset to reperfusion time compared with those treated in the same center. Age, sex, National Institutes of Health Stroke Scale score, and intubation did not affect delays.

Conclusions—Important delays were identified before reperfusion in the IMS III trial. Delays decreased as the trial progressed. Use of CT angiography and endovascular treatment in the same center were associated with time savings. These data may help in optimizing work flow in current and future endovascular trials.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424.

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Key Words: cerebrovascular disease ● infarction ● stroke

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The recent introduction of stentrievers resulted in higher rates of successful reperfusion, with procedure times reduced by more than half compared with prior techniques. For reperfusion therapies, attention to minimizing time to reperfusion via work flow improvement, targeting the various steps from emergency department (ED) arrival to microcatheter delivery at the thrombus interface, is paramount. Although some studies demonstrate the feasibility of shortening ED to intravenous tPA needle time to as short as 20 minutes, studies...
on work flow in stroke patients treated with endovascular therapies are scarce.

Multiple factors may contribute to considerable delays before endovascular reperfusion is achieved. Coordinating endovascular therapy is more complex given the resource requirement before treatment, variability in vascular access, and intensive nature of the procedures. With the multiple issues that require attention in the acute stroke setting, delays often go unrecognized by stroke team members, and potential strategies to reduce time to reperfusion may be overlooked.

To improve the various processes and to appropriately allocate resources, an understanding of the flow of patients through the hospital system from arrival to ED, the time loss associated with acquiring additional imaging, and the time of various components within the angiography suite until final reperfusion will be useful. In this study, we examine the patients in the endovascular arm of the Interventional Management of Stroke (IMS) III trial not only to evaluate the system processes but also to identify the factors that ultimately contribute to delays in achieving reperfusion.

**Methods**

The IMS III trial was an National Institutes of Health–funded, phase III, randomized, multicenter, open-label clinical trial designed to determine whether a combined approach with endovascular therapy after intravenous tPA is superior to standard intravenous therapy alone when initiated within 3 hours of acute stroke onset in moderate to severe strokes, as determined by a modified Rankin Scale score of 0 to 2 at 90 days. Patients were randomized in a 2:1 ratio, with more patients assigned to the endovascular arm.

The IMS III Trial enrolled 656 patients before enrollment was halted for futility in May 2012 on the basis of a recommendation by the Data and Safety Monitoring Board. The details of the study methods and results have been published previously. Of the 434 patients randomized to the endovascular arm, 16 patients were inpatients at the time of their strokes and were excluded from the work flow analysis. In the remaining 418 patients, the following time intervals were calculated: (1) stroke onset to ED arrival; (2) ED arrival to computed tomography (CT) start; (3) CT to start of intravenous tPA bolus; (4) intravenous tPA bolus to randomization; (5) randomization to groin puncture; (6) groin puncture to thrombus identification; (7) thrombus identification to start of endovascular therapy; and (8) start of endovascular therapy to reperfusion. Among those imaged with CT angiography (CTA), the CT to CTA times and CTA to start of intravenous tPA bolus times were also assessed.

The time of thrombus identification is defined as the time of the angiographic run that shows the intracranial occlusion. The time of start of endovascular therapy is the time of start of intra-arterial tPA bolus (via Micro-Sonic SV infusion system [EKOS] or a standard microcatheter), or the start time of balloon occlusion (if Merci retriever [Concentric Medical] was the primary intra-arterial device), or the start time of thrombus aspiration (if Penumbra system [Penumbra] was the primary intra-arterial device), or the time of first deployment of the device (if Solitaire FR [Covidien] was the primary intra-arterial device). The reperfusion time is the time of the last angiographic image.

The impacts of patient transfer, baseline CTA performance (yes versus no), intubation within 7 hours of onset (yes versus no), and time of randomization (working hours [Monday through Friday, 8 am to 5 pm] versus outside these hours) on the overall work flow time were evaluated. Patient transfer type was classified into those who received intravenous tPA and then transferred to another facility for endovascular therapy (“drip and ship”); those who were transferred to the endovascular facility before intravenous tPA initiation (“ship and drip”); and those who presented and treated within the same center (“mother-ship”). In addition, changes in times from ED to reperfusion and from groin puncture to reperfusion over the entire study period were assessed.

All times are reported as medians (with interquartile range [IQR]). The Kruskal-Wallis test was used to compare the median times, with adjustment for multiple comparisons by the Bonferroni method where applicable. To investigate factors associated with delays, univariable and multivariable linear regression models were constructed with both ED to reperfusion time and onset to reperfusion time individually as outcomes. Potential predictors include age, baseline National Institutes of Health Stroke Scale score stratum (≤19 versus ≥20), sex, warfarin use, quartiles of enrollment, randomization during working hours, transfer type, baseline use of CTA, and intubation status. The model for ED to reperfusion time was fit only within patients treated in the mother-ship paradigm and thus excluded transfer type as a predictor. Similarly, the impact of CTA conduct, patient transport, and enrollment time on favorable outcome (modified Rankin Scale score ≤2) was assessed in univariable and multivariable logistic regression models. Model assumptions and goodness of fit were assessed and found to be valid. Analyses were performed with the use of SAS 9.3 software. A 2-tailed significance level of 0.05 was used.

Informed consent was obtained from all participants (or their legal representatives) before enrollment. The study was approved by the institutional review committee of the participating centers.

**Results**

The clinical characteristics and outcomes of these patients were published previously. The specified time intervals are shown in Table 1. The median time from onset to ED arrival was 50 minutes (IQR 34). Before the start of the endovascular procedure, the longest time interval was from intravenous tPA initiation to groin puncture (85 minutes; IQR 41). During the endovascular procedure, the longest time interval was from start of endovascular therapy until the last angiographic image was acquired (85 minutes; IQR 74). There was a weak negative correlation between the time from onset to ED arrival with the onset to reperfusion time, and the median reperfusion time was 50 minutes (IQR 34). The time from ED to reperfusion time was 50 minutes (IQR 34) and the time from groin puncture to reperfusion was 85 minutes (IQR 74).

**Table 1.** Various Time Intervals in the Endovascular Arm of the Interventional Management of Stroke III Trial

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke onset to ED arrival (n=418)</td>
<td>50</td>
<td>34</td>
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<tr>
<td>ED arrival to CT start (n=413)</td>
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<td>15</td>
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<tr>
<td>CT to start of IV tPA bolus (n=412)</td>
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<tr>
<td>CT to start of IV tPA (patients with CTA, n=206)</td>
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<td>27</td>
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<tr>
<td>Randomization to groin puncture (n=408)</td>
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<td>Groin puncture to thrombus identification (n=327)</td>
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<td>Thrombus identification to start of endovascular therapy (n=310)</td>
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<td>Start of endovascular therapy to reperfusion (n=312)</td>
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<td>IV tPA bolus to groin puncture (n=407)</td>
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<tr>
<td>IV tPA bolus to endovascular therapy initiation (n=314)</td>
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<td>46</td>
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</table>

CT indicates computed tomography; CTA, computed tomographic angiography; ED, emergency department; IQR, interquartile range; IV, intravenous; and tPA, tissue plasminogen activator.
the puncture to reperfusion time and between the time interval from ED arrival to baseline CT with the CT to puncture time.

**Delays Attributable to Interhospital Patient Transfer**

Time from intravenous tPA bolus to groin puncture was affected by transfer status (Figure 1 and Table 2). This difference appears to be driven largely by the time from randomization to puncture because the time from intravenous bolus to randomization is not different according to transfer type. Patients who were treated in the drip and ship paradigm had a significantly longer time from intravenous tPA to puncture than the patients randomized and treated in the same facility (P<0.0001 for both the intravenous tPA bolus to puncture and randomization to puncture time intervals). There was no difference in the time from intravenous to puncture in patients who were treated in the ship and drip paradigm compared with those who were randomized and treated in the same facility (P>0.2 for both time intervals).

The odds of a good clinical outcome (modified Rankin Scale score ≤2) for subjects treated under the drip and ship paradigm are less than the odds for subjects treated under the mother-ship paradigm (odds ratio, 0.56; 95% confidence interval, 0.31–0.99; P=0.045). However, this association was not significant after adjustment for baseline CTA, age, baseline National Institutes of Health Stroke Scale score, baseline Alberta Stroke Program Early CT score, and reperfusion status. Given the small number of patients in the ship and drip model, a comparative outcome analysis of this group was not performed.

**Use of CTA**

The use of CTA before randomization was not mandatory. However, a total of 207 patients (49.5%) in the endovascular arm had baseline CTA performed. The median time from baseline CT to CTA was 6 minutes (IQR 7). The use of CTA did not cause delays in intravenous tPA bolus initiation. The median time from CT to intravenous tPA bolus in those who underwent CTA (39 minutes) was significantly shorter than in those who did not undergo CTA (47 minutes; Figure 2).

Patients who underwent CTA or magnetic resonance angiography had a slightly higher proportion of proximal occlusions compared with those who underwent CT alone, with internal carotid artery or M1 occlusions found in 66.9% in the CTA/magnetic resonance angiography group versus 61.0% in the CT alone group (P>0.05).

Transfer patients were less likely to have a baseline CTA and experienced a longer time from randomization to puncture. To minimize the impact of this potential confounding, the effect of baseline CTA use on favorable outcome was analyzed only under the mother-ship paradigm (Figure 3). The odds of favorable outcome among subjects with a baseline CTA were 2.1 times the odds for subjects with CT alone (95%
confidence interval, 1.1–3.8) after adjustment for age, baseline National Institutes of Health Stroke Scale score stratum, baseline Alberta Stroke Program Early CT score, site of occlusion, and successful reperfusion (defined as thrombolysis in cerebral infarction score 2b to 3).

**Intubation**

The overall work flow time did not vary significantly according to intubation utilization (Table I in the online-only Data Supplement). The median time from randomization to groin puncture was 60 minutes for those who did not require intubation (n=251 patients) compared with 66 minutes for those who were intubated according to the routine practice of that institution for endovascular therapy (n=73 patients) and 68 minutes for those who required intubation for medical reasons (n=67 patients).

**Delays Attributable to Procedural Timing**

Randomization occurred during working hours (Monday through Friday, 8 am to 5 pm) in 207 patients versus 211 patients randomized outside these hours (Figure 4). The ED to imaging time during working hours was 20 minutes (IQR 15 minutes) compared with 19 minutes in those treated outside these hours (IQR 15 minutes; P=0.20). The time from CT to

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*Figure 2.* Time intervals in patients investigated by computed tomography (CT) and computed tomographic angiography (CTA) vs CT alone. ED indicates emergency department; IA, start of endovascular therapy; ID, thrombus identification; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; Puncture, groin puncture; and Rand, randomization.

*Figure 3.* Time intervals in patients investigated by computed tomography (CT) and computed tomographic angiography (CTA) vs CT alone in the mother-ship paradigm only. ED indicates emergency department; IA, start of endovascular therapy; ID, thrombus identification; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; Puncture, groin puncture; and Rand, randomization.
groin puncture during working hours (119 minutes; IQR 49 minutes) was shorter than the 141 minutes for those presenting after these hours (IQR 54 minutes; \( P < 0.0001 \)). In those who were randomized during daytime (8 am to 9 pm), the time from CT to groin puncture was 127 minutes (n=341; IQR 51 minutes) compared with 142 minutes during nighttime (n=63; IQR 60 minutes; \( P = 0.0012 \)).

**Work Flow Changes During the Enrollment Period**

There was significant improvement in the time from ED arrival to reperfusion as well as the time from groin puncture to reperfusion during the course of the trial (Figure 5). During the first quartile of enrollment, the median time from ED arrival to reperfusion was 316 minutes compared with 246 minutes in the last quartile (\( P < 0.0001 \)). Similarly, the time from groin puncture to reperfusion decreased from 145 minutes during the first quartile of enrollment to 120 minutes in the last quartile (\( P=0.0005 \)).

**Predictors of Delays in ED Arrival to Reperfusion and Onset to Reperfusion Times**

A multivariable linear regression model was fitted to identify predictors of time from ED arrival to reperfusion in 261 patients without missing data who were treated in the same facility (mother-ship). Significant predictors were the use of CTA, procedural timing, and timing of enrollment during the course of the trial. Patients who underwent CTA had \( \approx 20 \) minutes shorter ED to reperfusion times compared with those who did not have CTA (\( P=0.008 \)). Similarly, patients who were randomized during working hours had 15 minutes shorter ED to reperfusion time compared with those who were randomized outside these hours (\( P=0.03 \)). Finally, patients who were enrolled during the last
quartile of the study had 46 minutes shorter ED to reperfusion time compared with patients who were enrolled during the first quartile of the study ($P<0.0001$). The ED to reperfusion times for patients enrolled in the second and third quartiles were not significantly different from those enrolled during the first quartile.

We also investigated factors that affected the onset to reperfusion times. Subjects with baseline CTA had 17 minutes shorter onset to reperfusion times compared with patients who did not have baseline CTA ($P=0.016$). Compared with patients who were enrolled during the first quartile of the study, patients who were enrolled during the last quartile had 42 minutes shorter onset to reperfusion time ($P<0.0001$). However, there was not a significant difference in the onset to reperfusion time between patients enrolled during the second or third quartiles and those enrolled in the first. Finally, patients treated in the drip and ship paradigm had 21 minutes longer onset to reperfusion time compared with those treated in the same center ($P=0.039$). There was insufficient evidence to demonstrate a longer onset to reperfusion time (mean 22 minutes) in those treated in the ship and drip paradigm compared with those treated in the same center ($P=0.16$); however, there are only 17 patients in this ship and drip category, resulting in limited power for this test. In these 2 models, age, sex, baseline National Institutes of Health Stroke Scale score, and intubation status were not shown to have significant impact on time delays.

**Discussion**

In acute ischemic stroke therapy with intravenous tPA, ED to needle time within 60 minutes has become an important benchmark in evaluating the efficiency of the work flow for delivering intravenous tPA and measuring the quality of stroke centers. Despite the evidence behind intravenous tPA and the resources allocated to meeting this target, only a quarter of intravenous tPA–treated patients met this time metric in “Get With the Guidelines.” Multiple target times have been proposed for endovascular therapy, including, for example, picture-to-puncture and puncture-to-reperfusion times. Certain time metrics capture delays at specific stages of the treatment continuum (eg, delays in patients’ transport are captured by the picture-to-puncture time). However, there is no consensus on a single time metric that would capture the elements unique to those treated with the combined approach of intravenous tPA plus endovascular therapy. Such time metric is increasingly needed to better understand these delays and to provide a target that all centers should aspire to achieve.

The importance of a fast onset to treatment time in acute ischemic stroke cannot be overemphasized. Considerable delays were encountered in starting endovascular therapy in the IMS III trial. Although 63.4% of the patients presented to the ED within 60 minutes, delays occurred from the start of intravenous tPA infusion to randomization, followed by further delays during the endovascular procedures until reperfusion was achieved. With the known strong correlation between time and stroke outcome, such delays are expected to produce lower than anticipated outcomes with endovascular therapy.

Although the time from ED arrival to endovascular reperfusion improved during the course of the trial, significant variability in the times within each enrollment quartile may have prevented these shorter times from reflecting on the overall trial results.

Some of the delays encountered during the endovascular procedures may be device related. The current first-choice endovascular device stentrieveries were used in only few patients in the endovascular arm, which may have affected both the success and speed of reperfusion. With the increasing use of stentrieveries and the progressively short puncture-to-reperfusion times reported, endovascular procedures are already shorter and yield higher rates of successful reperfusion.

Our data did not show a longer time to intravenous tPA administration when baseline CTA imaging was performed. When added to the other valuable information gained from CTA regarding the exact occlusion site and the vascular bed anatomy, CTA becomes an instrumental tool that will result in a net saving of time from onset to reperfusion. In addition to outlining the anatomic and pathological aspects of the aortic arch and carotid system to aid in planning the endovascular procedure, CTA also serves to localize the exact site of occlusion. It is not uncommon for a thalamic stroke attributable to posterior cerebral artery occlusion to mimic a middle cerebral artery occlusion or for a clinical right anterior cerebral artery occlusion to require endovascular access from the left carotid system when both anterior cerebral arteries originate from the left side (azygous variant). Moreover, CTA helps in planning the use of appropriate catheters and other tools and obviates the need for a complete angiogram and hence may serve to save procedural time. However, the association of CTA use with shorter time to reperfusion has other potential explanations. Routine CTA use is expected in large-volume centers where protocols for intravenous tPA use are practiced routinely with subsequent efficient and timely execution. In addition, the interpretation of CTA is anticipated to be faster in centers in which this imaging modality is used routinely. We did not measure the time required for CTA interpretation because of numerous practical and perceived difficulties. However, CTA has the advantage of being readily available on acquisition with no need for postprocessing. Moreover, interpretation of CTA images could take place in parallel with other treatment steps without delaying the overall work flow. Our data did not show a significantly longer time to groin puncture in patients who were intubated for the endovascular procedure. However, the time required for intubation may become a factor in patients treated with stentrieveries, in which case short imaging to reperfusion times are achievable. In addition, we did not investigate the effects of general anesthesia on stroke outcome in these patients.

Significant delays were noted from intravenous tPA administration to groin puncture in the IMS III study. There are many potential reasons for delays in this time interval. One component might be delays encountered during patient transport after intravenous tPA is initiated. Patients who received intravenous tPA in the drip and ship paradigm had longer times from tPA to groin puncture compared with those transported without receiving intravenous tPA. Although intravenous tPA therapy should be initiated as soon as possible in all eligible patients, this finding highlights the need for protocols to guide the care of patients planned for transport for endovascular stroke therapy to minimize any delays introduced by tPA administration before transportation. Prehospital assessment and triage of the most severe stroke patients directly to
comprehensive stroke centers that are experienced in endovascular therapy is another potential mechanism to decrease delays. To measure delays encountered during patient transfer, the American Heart Association defined a time metric (door-in/door-out) for patients with acute coronary syndrome to capture the time interval from admission to the outside hospital to ambulance departure toward the treatment center.22 When this metric was achieved in ≤30 minutes, faster treatment times and lower mortality were described. To account for delays encountered in the endovascular drip and ship approach, investigators devised the picture-to-puncture time metric to capture delays occurring from the time of baseline CT scan until groin puncture is done.15 Patients with a picture-to-puncture time >90 minutes had a significantly lower likelihood of independent functional recovery at 90 days. This stresses the importance of coordinated, protocol-driven steps for the expedited transport and treatment of such patients, particularly when imaging needs to be repeated before the endovascular procedure.

Delays from intravenous tPA administration to randomization were encountered in patients treated with endovascular therapy in the same center. Some of these delays can be attributed to the time spent screening the patient for the trial, obtaining of informed consent, and the randomization process. Such delays are well documented and occur despite best efforts.23 Deferral of consent, surrogate consent, or shortened consent forms have been proposed to shorten this time interval. Furthermore, the time required for the assembly of the interventional team, for intubation (in centers routinely performing these procedures under general anesthesia), and for preparing the endovascular devices can result in significant delays. Alerting the endovascular team as soon as possible, having an angiography tray ready for use, and using the same catheter/device setup for all endovascular stroke cases are measures that can be considered to decrease these delays. Comprehensive stroke centers with high patient volume might be more accustomed to these practices compared with centers with relatively low patient volume.

Patients treated after hours and on weekends had longer CT to groin puncture times compared with those treated in working or daytime hours. Worse in-hospital outcomes have been reported in stroke patients admitted during weekends compared with regular working hours.24,25 However, some studies suggest that comprehensive stroke centers seem to avoid this effect.26 This study has limitations. An inherent bias exists that people tend to function better when they are being watched or recorded. This may cause the times recorded in the setting of a trial to look better than real-life times. However, any time saved because of this bias is likely counteracted by times lost in obtaining trial consent. Our data and analysis of factors affecting work flow are restricted to the variables available in the study. Other variables that may influence time delay are not available for analysis, such as individual centers’ case volume and catchment area. We performed exploratory analyses to assess the impact of some of the factors we studied on outcomes. These post hoc analyses do not account for many important baseline differences that could explain any outcome difference. Therefore, the results of the outcome analyses should be viewed in the context of these important limitations, and we hope that they will serve to stimulate further research in this subject.

Conclusions

In the endovascular arm of the IMS III trial, there were significant delays from start of intravenous tPA to groin puncture. Improvement in workflow times were noted as the trial advanced. The use of CTA correlated with an overall shorter time to reperfusion and was associated with better clinical outcomes than in patients who underwent CT alone. Use of intubation did not result in additional delays. Endovascular treatment outside of working hours resulted in additional delays. These data may help in designing, optimizing, and documenting workflow in current and future endovascular trials.

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Disclosures

Dr Goyal received a modest research Grant from Covidien. He is a paid consultant for Covidien, has received lecture fees from Covidien, and owns stock in Calgary Scientific and NoNO. Dr Menon received research support from the Heart and Stroke Foundation of Canada Research Scholarship. Dr Demchuk received grant support and lecture fees from Covidien. Dr Hill received a research grant from Hoffman–La Roche Canada and the Heart and Stroke Foundation of Alberta. He is a paid consultant for the Verais Group. He received lecture fees from Hoffman–La Roche Canada and owns stock in Calgary Scientific. Dr Tomsick received a research grant from Covidien. Dr Khatri serves as an expert witness in medicolegal consulting. She is a paid consultant for Penumbra, Genentech, and Janssen Pharmaceuticals and has received travel support from Genentech. Dr Zaidat has nothing to disclose. Dr Jovin is a paid consultant for Silk Road Medical and owns stock in Silk Road Medical. Dr Broderick received lecture fees from Oakstone Publishing and consulting fees from PhotoThera. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

The significance of time in hyperacute ischemic stroke behooves the medical team to guarantee rapid work flow until reperfusion is achieved. The numerous and delicate steps involved require well-planned protocols to ensure the safe and smooth transition of patients from one stage to the next. The recent Interventional Management of Stroke (IMS) III randomized, controlled trial is the largest study to date to examine the efficacy of endovascular therapy against the standard treatment of intravenous tissue plasminogen activator. The IMS III study also offers valuable insights into the importance of work flow in ensuring timely reperfusion. In this article, the workflow of patients enrolled in the endovascular arm of IMS III is divided into different time intervals and analyzed to provide a better understanding of the sources and magnitude of delay. These findings will also inform current and future endovascular trials to accomplish an optimized work flow for their patients and thus faster reperfusion.
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Supplemental Table 1. Various times interval according to the status and indication for intubation.

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<th>Intubated</th>
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<td>IV Bolus to IA Therapy</td>
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