Door-to-Needle Time and the Proportion of Patients Receiving Intravenous Thrombolysis in Acute Ischemic Stroke

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Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) is one of very few effective treatments for acute ischemic stroke. Still, in most centers, only a small proportion (2%–7%) of patients with ischemic stroke receive this treatment in daily practice. The most important factor limiting IVT administration is time because it has to be administered within 4.5 hours of symptom onset. Even within this time window, the clinical benefit from IVT declines rapidly (time is brain), and every minute counts. If IVT is started within 90 minutes after stroke onset, the number of patients needed to treat to achieve an excellent clinical outcome modified Rankin scale score (0–1) is 4. Within the 180–270-minute time window, this number dramatically increases to 14. In other words, a shorter delay from symptom to IVT; the so-called symptom-to-needle time, can make the difference between being independent and being dependent. Reducing the symptom-to-needle time requires several hurdles to be jumped. Most time is lost in the prehospital period, the so-called symptom-to-door time to symptom-to-needle time, mainly because of patients waiting before they seek medical attention. However, this is difficult to accomplish because campaigns aimed at raising public awareness of stroke symptoms have only limited impact on behavior. Inside the hospital, focus should be on decreasing the time from arrival to IVT administration, the so-called door-to-needle time (DNT). Besides improved functional outcome, a reduced DNT will also increase the proportion of patients eligible for IVT because more patients can be treated before the 4.5-hour time limit. Unfortunately, >15 years after IVT was proven to be clinically effective, in most institutions, the DNT is still >60 minutes for the majority of patients. In most countries, national guidelines recommend that the DNT should not exceed this 60-minute limit. For example, a national initiative organized by the American Heart Association in partnership with other organizations aims to achieve a DNT ≤60 minutes for ≥50%, and the Safe Implementation of Treatments in Stroke Watch aims to reduce the DNT from a median of 65 minutes to <40 minutes for at least half of the patients. Moreover, the DNT is increasingly used by administrations as a performance measure to monitor quality of care and to compare performances between hospitals. Nonetheless, numerous studies and clinical trials are being undertaken to investigate elaborate strategies to enhance IVT efficacy or to select subgroups of patients suitable for IVT beyond the 4.5-hour time window. However, we think that focus should also be on what we know is best for these patients: reduction of the DNT. In contrast to stroke, in the majority of patients with acute myocardial infarction, fibrinolytic reperfusion can be applied with a DNT <30 minutes. It is hard to defend that for patients with acute ischemic stroke, the DNT is still more than twice as long. Streamlining triage, prenotification systems, computerized in-hospital alert systems, or placing the CT scanner near the emergency room are all measures that may reduce the DNT for patients with stroke. Indeed, recent studies have demonstrated that half of the patients can be treated within 20 minutes. Therefore, we advocate that in clinical stroke care, the focus should be on a reduction of the DNT. We realize that local differences such as case mix of patients can always impact the DNT. For example, not only ethnicity and sex but also stroke characteristics such as posterior circulation stroke can influence the DNT. However, the DNT provides valuable insight in local trends and can serve as a performance measure to improve quality of care, not only by comparing results of one institution over time but also by comparison with other centers nationwide or internationally. A prerequisite for such comparisons is that the DNT is...
recorded and interpreted uniformly. Besides its use as a performance measure, an additional advantage of a uniform DNT registration is facilitation of future research aiming to improve the DNT.

At first sight, the definition and the interpretation of the DNT seems unequivocal, but in clinical practice, this is not the case. We assembled an international panel of leading stroke specialists to discuss the ambiguities that can arise with current definitions and propose a definition that leaves no room for interhospital differences in documentation of the DNT.

In addition to the DNT, the proportion of patients treated with IVT can also serve as an important performance measure. Currently, the definition of the denominator of this proportion differs between studies. We discuss these differences and propose a standard definition to facilitate uniform documentation. We did not use a formal (eg, Delphi) procedure to reach consensus because our topic does not concern lack of evidence or contradictory evidence. However, except for anonymity of the participants, we followed the key characteristics of the Delphi method such as a structured flow of information to a facilitator (N.D.K.) and regular feedback.

The Door-to-Needle Time: Definition and Interpretation

The Door

The door, the moment that the clock starts ticking for the DNT, seems to be documented in various ways in clinical practice. For example, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST registry) uses “the moment the patient entered the facility,” whereas the Get With The Guidelines—Stroke of the American Heart Association uses “the moment after the patient was triaged and considered to have a stroke,” and other published studies use “the moment of presentation to the emergency department” or “the moment of stroke unit admission.” Moreover, regional differences in stroke care can also lead to considerable differences in the DNT because it can be unclear how the door is defined. For example, in some countries, patients with acute stroke are first seen in accident and emergency departments to undergo diagnostics including a CT scan. Subsequently, especially if telestroke support is not provided, these patients are transported to another facility for IVT. When the clock starts ticking on arrival at this second facility, this would lead to an artificially short DNT. Therefore, we propose to define the start of the DNT as the moment the stroke patient first enters the door of the first facility. In most hospitals, this is the entrance door of the emergency room, but as in the above example, this can also be the door of another facility. As such, educating staff in the emergency room to recognize stroke symptoms and to act accordingly and improving regional agreements will be an incentive for neurologists or stroke specialists to improve the DNT. In clinical practice, logistic problems such as delays in booking patients into the system during busy hours in the emergency room can significantly distort the actual arrival time. This has to be taken into account, and if indeed this seems to be a problem, a separate registration for IVT patients should be considered. For patients already hospitalized outside the neurology department or stroke unit at the moment of stroke onset, for instance, on a cardiology ward, this definition cannot be used because these patients have already entered the facility before stroke onset. Therefore, for this (small) subgroup, we propose to define the start of the DNT as the moment of first consultation of the neurologist. Generally, this will be the telephone call received by the neurologist or stroke physician on duty that there is a patient with a suspected stroke. However, because in these patients, the whole symptom-to-needle time is completely in-hospital care, we suggest separately recording the onset of stroke symptoms because it could help to identify departments that need additional education in recognizing stroke symptoms.

Time to Needle—Patient and Logistic Factors

Difficult to Draw Apart

The Time

The in-hospital route from the door to the needle is potentially prolonged by various patient-related and logistic factors (see Table 1), such as uncertainty of symptom onset, a too high blood pressure to start IVT, or incorrect triage. Ideally, as a performance measure, the DNT should not depend on patient-related factors because the caregivers cannot influence these. This may lead to a policy in which instead of the DNT, the time until a patient could have been treated with IVT is recorded, the so-called time to intention to needle. However, this could lead to the concealment of logistic factors that impede rapid IVT. For example, when IVT is renounced because of a fluctuating neurological deficit (or any other patient-related factor listed in Table 1) and the time to intention to needle is recorded, further logistic steps such as transportation or weighing of the patient, and the corresponding time windows, are lost. To what extend the DNT will be influenced by patient-related factors will differ between hospitals, depending on local protocols and policies. For example, uncontrolled blood pressure contraindicating IVT will actively be lowered in some hospitals and as such lengthen the DNT, whereas in other hospitals, the same patient would not be treated with IVT at all, and as such not affect the DNT. Other examples are so-called wake-up strokes or when there is a suspicion of a

Table 1.

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th>Logistic Factors</th>
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<tr>
<td>Uncertain when symptoms started</td>
<td>Incorrect triage</td>
</tr>
<tr>
<td>Unknown medical history</td>
<td>Insufficient personnel (nursing/supervision)</td>
</tr>
<tr>
<td>Uncontrolled blood pressure</td>
<td>Difficulties with drip or catheter insertion</td>
</tr>
<tr>
<td>Fluctuating neurological deficit</td>
<td>Difficulties with weighing the patient</td>
</tr>
<tr>
<td>Patient has to undergo other treatment before IVT</td>
<td>CT scan occupied</td>
</tr>
<tr>
<td>Uncertainty on (anti-)coagulation status</td>
<td>Technical problems</td>
</tr>
<tr>
<td>• with equipment</td>
<td>• with IT network</td>
</tr>
<tr>
<td>• with IT network</td>
<td>Laboratory results delayed</td>
</tr>
<tr>
<td>No medication available</td>
<td>Waiting for consent from patient or family</td>
</tr>
<tr>
<td>Patient transferred from another institution</td>
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IT indicates information technology; and IVT, intravenous thrombolysis.
stroke mimic, resulting in additional (imaging) investigations with subsequent lengthening of the DNT. Thus, it is important to realize that a longer DNT could also reflect meticulous IVT treatment. Another example is when there is initial uncertainty about the exact time of symptom onset, additional time investment in history taking could result in a positive decision about IVT, but it also results in a longer DNT. There will always be outliers with large DNTs, but this group will be relatively small with modest impact on the median DNT. Reviewing these outliers is important because potentially modifiable factors can be detected that prolong the DNT. As an example, registration could reveal that the DNT is prolonged substantially by waiting for the blood sample test for the international normalized ratio. This could instigate the search for a faster way of doing this, such as a capillary blood measurements system of the international normalized ratio, thereby substantially reducing the DNT. Prospective documentation of the factors mentioned in Table 1 could facilitate to identify these factors. It could also be of importance to review outliers with a very short DNT because this might reflect dangerous practice in which contraindications are ignored.

The Needle
Although the needle, defined as the moment the rt-PA treatment is administered, seems clear, in clinical practice, even this part of the definition of the DNT can be ambiguous. According to the original trial from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, rt-PA (0.9 mg/kg) has to be administered as a 10% bolus followed by delivery of the remaining 90% as a constant infusion during a period of 60 minutes.23 We have noticed that in clinical practice, an extra time window is introduced between the administration of the bolus and the continuous infusion, which is used to perform actions such as weighing or transporting of the patient from the emergency room or CT scanner to the stroke unit. Indeed, weighing patients with neurological deficits may be time consuming but weight estimation leads to ≈20% underestimation or overestimation.24 Accurate weighing is important because a higher dose of rt-PA per kilogram leads to more bleeding complications.24,25 Also, there is a pharmacological rationale not delaying the infusion after the bolus. The bolus results in a rapid high plasma concentration that declines rapidly because of binding to fibrin and distribution of the drug, resulting in a short half-life time (4–5 minutes).26 Delaying the subsequent infusion could therefore result in a rapid decline in plasma concentration, probably rendering IVT less efficient.27,28 Reducing the DNT by introducing a delay between the bolus and the infusion should therefore be discouraged. Consequently, we define the end point of the DNT as the moment the IV bolus with rt-PA is administered, provided that this is followed immediately by administration of the continuous infusion (Table 2).

Reporting the Door-to-Needle Time
The DNT will likely be distributed nonparametrically. Therefore, we propose to report the DNT as a median value with interquartile ranges and extremes (<10% or >90%) rather than a mean value with a standard deviation. For local use, a scatter plot is probably the most useful in our experience.
onset, no patients are excluded a priori from IVT. Inclusion of all patients presenting within 4.5 hours of symptom onset will overestimate the denominator because those presenting right before 4.5 hours will not have time to be assessed and scanned. We also understand that the IVT rate will never be 100%. For example, in everyday practice, some patients with little or no neurological deficit will still be admitted. If this group seems to be large, this should trigger re-evaluation of local policies because it could reflect too much reservation in administering IVT. It is therefore important to document the reason(s) a patient was not treated with IVT. Also, it is important to note that the time window may change over time because new information from randomized clinical trials becomes available. For example, initially, IVT was only proven till 3 hours after symptom onset, and more recently, publication of the International Stroke Trial (IST-3) led in guidelines of some countries to consider treatment between 4.5 and 6 hours on an individual basis. To avoid discussion, we chose to adopt the current international guidelines and to apply to the largest group of patients (0–4.5 hours) for this first proposed uniform DNT definition. It should be realized that the threshold of 4.5 hours is a bit arbitrary and introduces an underestimation of appropriate IVT rates when analyzing data before the extension from the 3- to 4.5-hour-time window for IVT. Another point is that some patients will have a final diagnosis other than acute ischemic stroke. Although in experienced stroke centers, these so-called stroke mimics occur in <2%, in less-experienced centers, this percentage could be higher, and one might consider using the thrombolysis rate for this particular patient group as a secondary performance measure.

Conclusions

Significant clinical gain in acute stroke care can be achieved relatively easily, first, by simply implementing what we already know what is best: to reduce the DNT. If documented uniformly, the DNT is useful as a performance measure to detect bottlenecks impeding rapid IVT treatment and to reveal temporal trends and differences between institutions. This performance measure could be easily compared between different centers, organizing structures, and countries if uniformly defined. In this article, we have proposed a uniform definition of the DNT: starting the moment the patient first enters the first facility and ending when the IV bolus with rt-PA is administered, provided that this is followed immediately by the administration of the continuous rt-PA infusion. Besides the DNT, the IVT rate could be an important performance measure, although it has to be interpreted with caution because it can be subject to population and referral bias. As for the DNT, a uniform way to construct the denominator in this proportion is important: all patients admitted with ischemic stroke, within 4.5 hours from symptom onset.

With this article, which is endorsed by an international panel of leading stroke specialists, we propose recommendations for performance measures for IVT. Further work on this issue might be a useful task for organizations such as the European Stroke Organization or the American Stroke Association.

Acknowledgments

Authorship contribution is as follows: Drs Kruyt and Roos designed the first draft and reviewed all subsequent drafts and the final article. Dr Kruyt facilitated regular feedback to the separate authors. All other authors contributed equally, reviewing all drafts and the final article.

Disclosures

None.

References

3. van Wijngaarden JD, Dirks M, Niessen LW, Huisman R, Dippel DW. Do centres with well-developed protocols, training and infrastructure have higher rates of thrombolysis for acute ischaemic stroke? QJM. 2011;104:785–791.


**Key Words:** door-to-needle time ■ performance measure ■ stroke ■ thrombolytic therapy
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#### Appendix

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<tr>
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