**Abstract:**

Introduction: Stroke is a development of an acute focal neurological deficit with an ischemic or hemorrhagic origin. Thrombolysis within 4.5 hours of ischemic stroke onset improves outcome. Guidelines recommend administration of intravenous recombinant tissue plasminogen activator within 60 minutes upon arrival at the hospital, meaning the door-to-needle time (DNT) should be less than 60 minutes. In this study, a stroke protocol was introduced at the emergency department of the Ghent University Hospital with as primary goal to shorten the DNT. Methodology: This study was an uncontrolled before-after cohort study. A "Code Stroke" protocol (CSP) was implemented and the results from the pre-code stroke protocol period (Pre-CSP period, from August 15th, 2016 until March 5th, 2017) were compared with the results from the post-code stroke protocol period (Post-CSP period, from March 6th, 2017 until July 16th, 2017). Results: The median DNT decreased significantly from 57 minutes in the Pre-CSP period to 33 minutes in the Post-CSP period (p < 0.001). The door-to-triage time (DTT), triage-to-emergency physician time (TET), emergency physician-to-CT time (ECT) and CT-to-needle time (CNT) decreased significantly Post-CSP compared to Pre-CSP. When adjusting the results for other variables that might have an influence on these time intervals, the TET, ECT and CNT also decreased significantly. There was a statistically significant effect of the implementation of the CSP on the number of patients treated with a DNT within 20, 30, 45 and 60 minutes (p = 0.008). Conclusion: A significant decrease in DNT can be achieved with the implementation of this stroke protocol.
Impact of a code stroke protocol on the door-to-needle time for IV thrombolysis: a feasibility study

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Abstract:
Introduction: Stroke is a development of an acute focal neurological deficit with an ischemic or hemorrhagic origin. Thrombolysis within 4.5 hours of ischemic stroke onset improves outcome. Guidelines recommend administration of intravenous recombinant tissue plasminogen activator within 60 minutes upon arrival at the hospital, meaning the door-to-needle time (DNT) should be less than 60 minutes. In this study, a stroke protocol was introduced at the emergency department of the Ghent University Hospital with as primary goal to shorten the DNT. Methodology: This study was an uncontrolled before-after cohort study. A “Code Stroke” protocol (CSP) was implemented and the results from the pre-code stroke protocol period (Pre-CSP period, from August 15th, 2016 until March 5th, 2017) were compared with the results from the post-code stroke protocol period (Post-CSP period, from March 6th, 2017 until July 16th, 2017). Results: The median DNT decreased significantly from 57 minutes in the Pre-CSP period to 33 minutes in the Post-CSP period (p < 0.001). The door-to-triage time (DTT), triage-to-emergency physician time (TET), emergency physician-to-CT time (ECT) and CT-to needle time (CNT) decreased significantly Post-CSP compared to Pre-CSP. When adjusting the results for other variables that might have an influence on these time intervals, the TET, ECT and CNT also decreased significantly. There was a statistically significant effect of the implementation of the CSP on the number of patients treated with a DNT within 20, 30, 45 and 60 minutes (p = 0.008). Conclusion: A significant decrease in DNT can be achieved with the implementation of this stroke protocol.

Key words:
Stroke; protocol; thrombolysis; door-to-needle time; emergency department
Impact of a code stroke protocol on the door-to-needle time for IV thrombolysis: a feasibility study
Introduction

Stroke is a development of an acute focal neurological deficit, due to a disturbance of the blood supply to the brain. It can be either ischemic or hemorrhagic. It is one of the major causes of morbidity and mortality worldwide. (1) Intravenous thrombolysis within 4.5 hours of ischemic stroke onset improves outcome. These benefits are time-dependent; the earlier the treatment the greater the benefit. (2) Because of these time-dependent benefits, guidelines recommend administration of recombinant tissue plasminogen activator (rt-PA) within 60 minutes upon arrival at the hospital, meaning door-to-needle time (DNT) should be less than 60 minutes. (2) Despite these recommendations, studies show that less than one third of the patients with an acute ischemic stroke are treated within this 60 minutes timeframe. (3) The last years, different studies have shown that implementation of a stroke-specific protocol lead to a significant improvement in DNT and hence the neurological recovery. (4-7) On March 6th, 2017, a “Code Stroke” protocol (CSP) was introduced at the emergency department of the Ghent University Hospital with as primary goal to shorten the DNT.

Methodology

Design and Population

This study is an uncontrolled before-after cohort study; the pre-code stroke protocol period (Pre-CSP period, from August 15th, 2016 until March 5th, 2017) versus the post-code stroke protocol period (Post-CSP period, from March 6th, 2017 until July 16th, 2017). All patients with acute focal neurological deficits admitted at the emergency department between August 15th, 2016 and July 16th, 2017 were enrolled. Patients could arrive at the emergency department by ambulance, referred by primary care physicians or by self-referral. Patients with acute focal neurological deficits transferred from other hospitals were excluded. There were no age
limitations. This study was approved by the Ethics Committee of the Ghent University Hospital (number of the ethical approval: B670201630038).

**Intervention**

The study intervention consisted of the implementation of a code stroke protocol. Before the start of the implementation, educational sessions were organized for all emergency department staff involved which included the recognition of an acute stroke using the balance, eyes, face, arm, speech, time (BE-FAST) scale and the importance of rapid treatment. The stroke protocol consisted of multiple interventions. For all patients admitted at the emergency department with an acute focal neurological deficit, a ‘code stroke’ was activated at triage. Once the alarm was activated, all involved team members got a spoken message on their pager which informed them about a potential acute stroke patient that might require thrombolysis. The team consisted of a neurologist, a radiologist, an emergency physician, an emergency supervising physician, an emergency nurse and a coordinating emergency nurse. Simultaneously the patient was examined by the emergency physician, the medical history and medication use was obtained and the nurse took a blood sample (with a point-of-care testing (POCT) for glucose) and monitored the vital signs. When the emergency physician confirmed acute focal neurological deficit, a standard CT protocol was requested without consulting the neurologist. This CT protocol consisted of a non-contrast and contrast brain CT scan with CT angiography of the circle of Willis and carotid arteries and perfusion CT scan of the brain. Standard stroke orders for the CT scan and laboratory test were electronically available. Upon receiving the code stroke, the radiologist made the CT room available for the patient. The neurologist came immediately to the emergency room to perform a neurologic examination. He accompanied the patient to the CT room together with the emergency nurse who took the rt-PA to the CT room. If the non-contrast brain CT scan showed no intracerebral hemorrhage and the
patient was eligible for drug administration, the bolus rt-PA was administered at the CT room. When a patient with an acute focal neurological deficit was brought to the emergency department by ambulance, a pre-alert of the code stroke was activated if the ambulance staff gave a prenotification to the hospital. Again, all the involved team members got alerted. This stroke protocol could be activated every day of the week, during day- and nighttime, with the exception that the neurologist had to be alerted via the cellular phone during nighttime since they are on call duty during the nightshift.

Data collection and definitions

From August 15th, 2016 until July 16th, 2017 data were prospectively collected from all the patients arriving at the emergency department with an acute focal neurological deficit. An ‘acute’ focal neurological deficit was defined as a focal neurological deficit of less than 6 hours duration or the first 6 hours after awaking with a wake-up stroke. Time of admission to the emergency department, triage, emergency physician consult, neurologist consult, CT scan and thrombolysis were noted. The different time intervals were derived from these times; door-to-triage time (DTT, the time from admission until triage), triage-to-emergency-physician time (TET, the time from triage until the evaluation by an emergency physician), emergency physician-to-CT time (ECT, the time from the evaluation by an emergency physician until the moment the patient arrives at the CT room), CT-to-needle time (CNT, the time from the moment the patient arrives at the CT room until the administration of the bolus rt-PA) and door-to-needle time (DNT, the time from admission until the administration of the bolus rt-PA). The times from the emergency physician to the neurologist and from the neurologist to the CT were not considered because it was not necessary to wait for the evaluation by a neurologist after the evaluation of an emergency physician to start the CT scan. The way the patients arrived at the emergency department (by ambulance or by self-transportation), the crowdedness at the
emergency department, the emergency department staffing (we divided the 24 hours depending on the staffing rather than on day and night; daytime staffing from 7:00 until 22:00 when approximately 5 emergency physicians and 8 nurses are working and nighttime staffing from 22:00 until 7:00 when approximately 2 emergency physicians and 4 nurses are working), the availability of the neurologist (in-hospital or on call), the place where rt-PA was administered (at the CT room or at the emergency department), the day of the week (weekday or weekend), the result of the CT scan and possible other treatments were also reported. Finally, the causes of obvious delays in time were registered.

*Primary and secondary outcomes*

The primary outcome was the effect of the implementation of the CSP on the DNT. Secondary outcome was the effect of the implementation of the stroke protocol on the other time intervals (DTT, TET, ECT and CNT) and the influence of specific variables on these time intervals (the medical transportation, the crowdedness at the emergency department, the emergency department staffing, the availability of the neurologist, the place where rt-PA was administered and the day of the week). The percentage of patients treated with a DNT within 20, 30, 45 and 60 min. Pre- and Post-CSP implementation were also analyzed.

*Statistical analysis*

Baseline characteristics Pre- and Post-CSP implementation were compared using the \( \chi^2 \) test for categorical variables and the Mann-Whitney U test for non-parametric continuous variables. Categorical variables were presented as numbers and percentages, non-parametric continuous variables as median and interquartile range (IQR). The DNT as well as the other time intervals (DTT, TET, ECT and CNT) were analyzed between the two groups with the Mann-Whitney U test and reported as median and IQR. Spearman’s correlation coefficient was used to identify
non-parametric continuous variables that have an influence on the different time intervals and the Mann-Whitney U test for the categorical variables. Linear regression analysis was used to analyze the effect of the implementation of the CSP on the different time intervals adjusted for the confounding specific variables. The effect of the implementation of the CSP on the number of patients treated with a DNT within 20, 30, 45 and 60 minutes was reported and analyzed using the $\chi^2$ test. P-values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS version 24.0 software.

Results

Baseline Characteristics

From August 15th, 2016 until July 16th, 2017, 181 patients were enrolled in this study, of whom 110 (60,8%) in the Pre-CSP period and 71 (39,2%) in the Post-CSP period. In the Pre-CSP period 74 patients (67,3%) had the diagnosis of an acute ischemic stroke, compared to 47 patients (66,2%) in the Post-CSP period. After exclusion of the patients who were not eligible for thrombolysis, 39 patients (35,5%) with an acute ischemic stroke received rt-PA in the Pre-CSP period, compared to 29 patients (40,9%) in the Post-CSP period (Figure 1). Baseline characteristics of the patients enrolled in this study were similar between the Pre-CSP period and Post-CSP period and are presented in Table 1.

(Input Figure 1)

(Input Table 1)
Primary Outcome Analysis

The median DNT decreased significantly from 57 minutes (IQR 43 to 69 minutes) in the Pre-CSP period to 33 minutes (IQR 25 to 45 minutes) in the Post-CSP period (p < 0.001) (- Table 2).

(Input Table 2)

Secondary Outcome Analysis

The DTT, TET, ECT and CNT decreased significantly Post-CSP compared to Pre-CSP. The median times and IQR are presented in - Table 2.

There was a significant correlation between the crowdedness at the emergency department and the DTT and TET, but not with the ECT, CNT nor with the DNT. The medical transportation was significantly correlated with the DTT, TET, ECT and DNT, although not significantly correlated with the CNT. The place where rt-PA was administered was significantly correlated with the CNT and the DNT. The availability of the neurologist, the emergency department staffing or even the day of the week had no influence on the time intervals DTT, TET, ECT, CNT or DNT (- Table 3).

(Input Table 3)

Linear regression showed no longer a significant correlation between the DTT and the implementation of the CSP after adjustment for the crowdedness and the medical transportation, but there still was a significant correlation for the TET. The ECT had also a significant correlation with the stroke protocol after adjustment for the medical transportation,
as does the CNT after adjustment for the place of administration of rt-PA and the DNT after adjustment for the medical transportation and the place of administration of rt-PA (- Table 4).

(Input Table 4)

There was a statistically significant effect of the implementation of the stroke protocol on the number of patients treated with a DNT within 20, 30, 45 and 60 minutes (p = 0.008). The percentage of patients treated within 60 minutes increased significantly from 56.4% Pre-CSP to 86.1% Post-CSP (p = 0.009). 75.8% of patients were even treated within 45 minutes Post-CSP compared with 30.8% Pre-CSP (p < 0.001). Error! Reference source not found. gives an overview of those amounts Pre-CSP compared with Post-CSP.

(Input Figure 2)

DISCUSSION
The median DNT in our study decreased significantly from 57 minutes (IQR 43 to 69 minutes) to 33 minutes (IQR 25 to 45 minutes) (- Table 2). This is in line with the results of other studies. (4-7) In 2010, the American Heart Association/American Stroke Association launched the Target: Stroke Initiative. The final goal was to treat at least 50% of the patients with an acute ischemic stroke with rt-PA within 60 minutes upon arrival to the hospital. (2) In 2014, they introduced Target: Stroke Phase II, with as final goal to treat at least 75% of the patients with an acute ischemic stroke with rt-PA within 60 minutes and as secondary goal to treat at least 50% of the patients with an acute ischemic stroke with rt-PA within 45 minutes. (9) Our study showed a statistically significant increase of the proportion of patients treated within 60 minutes, from 56.4% Pre-CSP to 86.1% Post-CSP and an increase of the proportion of patients
treated within 45 minutes, from 30.8% Pre-CSP to 75.8% Post-CSP (Error! Reference source not found.). We can conclude that with the implementation of our CSP we met the criteria according to the American Heart Association/American Stroke Association. (2) Other studies also achieved this goal of having at least 75% of the patients with an acute ischemic stroke treated with rt-PA within 60 minutes after implementation of a CSP; 94% of the patients were treated within 60 minutes in a Finnish study in 2012 (4), 80% of the patients who arrived during the business hours were treated within 60 minutes in an Australian study (5), in a Dutch study in 2014, 98.9% of the patients were treated with rt-PA within 60 minutes in the immediate post-intervention period and 94.1% in the late post-intervention period. (6) In a Dutch study in 2016, 91.7% of the patients were treated within 60 minutes after implementation of a CSP. (7) In our study 10.3% of the patients were treated with rt-PA within 20 minutes. The Finnish study achieved much better results in 2012 where 50% of the patients were treated within 20 minutes, although in this study it was the result of 12 measures that have been systematically implemented over 13 years. (4) In the Dutch study of 2014, 15.6% of the patients were treated within 20 minutes in the immediate post-intervention period and 35.1% in the late post-intervention period. (6) In our study 41.3% of the patients were treated within 30 minutes, compared to 62.7% of the patients in the Dutch study of 2016. (7) So, although with the implementation of our stroke protocol we achieve good results that are within the expectations of the American Heart Association/American Stroke Association, still we do need to ameliorate our protocol to achieve results comparable to others (4-7).

When focusing on the stroke protocols of these previous studies, there are some interventions we did not incorporate in our stroke protocol which may be important to further reduce the DNT. The most important intervention is the direct transfer to the CT room upon arrival at the hospital. (4-7). Other important interventions are POCT-INR if applicable (4-7), advanced imaging only for selected patients or following the start of IV thrombolysis (4, 5, 7), preparing
rt-PA prior to patient arrival for highly suspect thrombolysis candidates (4), drawing routine blood samples after initiation of rt-PA (5) and using beds with built-in scales for exact weight determination (7). It is worth to consider implementing these interventions in our CSP to further improve our median DNT. Furthermore, there are some adaptations we can make based on our current experience. It occurs quite often that an ECG is taken before the patient goes to the CT room. Here, valuable and unnecessary minutes are lost. It is also difficult to allocate one patient to one dedicated emergency nurse; a potential solution would be to integrate a stroke unit nurse in our stroke team and get him/her involved as quick as possible. There are also some factors that we cannot influence. First, when a patient arrives at the emergency department by self-transportation, there is no possibility to triage him earlier, he should wait until earlier arrived patients get triaged first. Second, sometimes concomitant urgent patients can arrive at the emergency department, also needing an urgent CT scan (polytrauma patients, aortic dissection,…). In that case, our patient will have to wait, or will have to go to another (further located) CT room. And finally, our institution is a teaching hospital, meaning – in case of fluctuating or unclear neurological deficits – the emergency physician or the neurologist needs to get advice from his supervisor, which could take valuable minutes before rt-PA could be administered.

Our study has several limitations. First, this is an uncontrolled before-after cohort study. In this type of study design, there is always the possibility to overestimate the effectiveness of the investigated intervention. We tried to minimize bias by analyzing other possible contributing factors (such as medical transportation and crowdedness) and using Pre-CSP and Post-CSP groups with similar baseline characteristics. Second, we didn’t analyze thrombolysis-related complications. We can assume that a proportion of patients that were treated with rt-PA in a system with a good functioning stroke protocol, may have had symptoms that would have
resolved spontaneously if some more time would have expired. In our study 25.7% of the patients with an acute ischemic stroke had a transient ischemic attack (TIA) in the Pre-CSP period, compared with 17% in the Post-CSP period. It is possible that the number of patients with a TIA in the Post-CSP period would have been larger if we did not administer rt-PA that early. More patients treated with rt-PA also means that more patients have a possibility to develop symptomatic intracerebral hemorrhage (sICH), the most common drug related complication (10). But since sICH occurs significantly less frequently when the rt-PA is administered within the 60 min upon arrival, there is no evidence to delay the administration. (3) Third, outcomes were not analyzed in our study, meaning earlier treatment may not necessarily be correlated with a better outcome. Previous studies showed that a faster treatment is related to a better outcome, so we can assume that our patients would have benefit the earlier treatment. (11) Fourth, because the interventions of the stroke protocol were introduced all at once, it is difficult to determine which intervention was the key factor in reducing DNT. Fifth, the number of patients included in our study is rather small. However, even with these small numbers we do achieve statistically significant results.

There are several strengths of our study; we used a prospective study design and we used linear regression analysis to adjust for other contributing factors than the stroke protocol itself. The stroke protocol can easily be continued and it is applicable during the day and night.

To summarize, the implementation of the CSP contributed to a significant decrease in DNT, but implementing other interventions might further improve our results.
REFERENCES


- **Figure 1. Flowchart of patients included in the study.** Values are given in absolute numbers (percentages). Abbreviations: Pre-CSP, pre-code stroke protocol; Post-CSP, post-code stroke protocol; TIA, transient ischemic attack.

- **Figure 2: Number (%) of patients treated within 20, 30, 45 and 60 minutes (A) and number (%) of patients with DNT < 60 minutes and DNT < 45 minutes (B).**

- **Table 1: Baseline characteristics.** Abbreviations: Pre-CSP, pre-code stroke protocol; Post-CSP, post-code stroke protocol; IQR, interquartile range; rt-PA, recombinant tissue plasminogen activator. † Groups were compared by Mann-Whitney U tests ‡ Groups were compared by chi-square tests.

- **Table 2: Analysis of the different time intervals.** Values are given in minutes. Abbreviations: DNT, door-to-needle time; DTT, door-to-triage time; TET, triage-to-emergency physician time; ECT, emergency physician-to-CT time; CNT, CT-to-needle time; Pre-CSP, pre-code stroke protocol; Post-CSP, post-code stroke protocol; IQR, interquartile range. * Statistically significant p<0,05.

- **Table 3: Analysis of specific variables that have an influence on the different time intervals analyzed with Spearman’s correlation (A) and with Mann-Whitney U test (B).** Time values are given in minutes. Abbreviations: DNT, door-to-needle time; DTT, door-to-triage time; TET, triage-to-emergency physician time; ECT, emergency physician-to-CT time; CNT, CT-to-needle time; rt-PA, recombinant tissue plasminogen activator. * Statistically significant p<0,05. ♦ Statistically significant p<0,05, although not of value because the place of administration is situated further in the timeline of processes.

- **Table 4: Linear regression analysis of the different time intervals adjusted for the specific variables.** Values are given in minutes. Abbreviations: DTT, door-to-triage time; TET, triage-to-emergency physician time; ECT, emergency physician-to-CT time; CNT, CT-to-needle time; DNT, door-to-needle time; B, regression coefficient in minutes; CI, 95%
confidence interval; Pre-CSP, pre-code stroke protocol; Post-CSP, post-code stroke protocol. * Statistically significant p<0.05. + This parameter is set to zero because it is redundant. a p-value adjusted for crowdedness and medical transportation. b p-value adjusted for medical transportation. c p-value adjusted for place administration rt-PA. d p-value adjusted for medical transportation and place administration rt-PA.
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<td>CNT</td>
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</tr>
<tr>
<td>By ambulance</td>
<td>p=0.001</td>
<td>2 (0–7)</td>
</tr>
<tr>
<td>By self-transport</td>
<td>p=0.04</td>
<td>18 (12–7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Place administration rt</th>
<th>In-house</th>
<th>Emergency room</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>p=0.027</td>
<td>1 (0–0.5)</td>
</tr>
<tr>
<td>CT room</td>
<td>p=0.062</td>
<td>2 (0–2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Availability of neurologist</th>
<th>In-house</th>
<th>On call</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-house</td>
<td>p=0.066</td>
<td>2 (0–6)</td>
</tr>
<tr>
<td>On call</td>
<td>p=0.002</td>
<td>2 (0–10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Staffing</th>
<th>Dayshift</th>
<th>Nightshift</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.077</td>
<td>2 (0–6)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>p=0.062</td>
<td>3 (0–10)</td>
<td>0 (0–5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day of the week</th>
<th>Weekday</th>
<th>Weekend</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.241</td>
<td>2 (0–6)</td>
<td>1 (0–0.5)</td>
</tr>
<tr>
<td>p=0.903</td>
<td>3 (0–9)</td>
<td>2 (0–1)</td>
</tr>
<tr>
<td>Protocol</td>
<td>Pre-CPSP</td>
<td>Post-CPSP</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>DT</td>
<td>0.0004</td>
<td>17 0.02</td>
</tr>
<tr>
<td>CI</td>
<td>0.326</td>
<td>0.001</td>
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</tbody>
</table>

Table 4