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Relationship Between Onset-to-Door Time and Door-to-Thrombolysis Time

A Pooled Analysis of 10 Dedicated Stroke Centers

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Background and Purpose—Inverse relationship between onset-to-door time (ODT) and door-to-needle time (DNT) in stroke thrombolysis was reported from various registries. We analyzed this relationship and other determinants of DNT in dedicated stroke centers.

Methods—Prospectively collected data of consecutive ischemic stroke patients from 10 centers who received IV thrombolysis within 4.5 hours from symptom onset were merged (n=7106). DNT was analyzed as a function of demographic and prehospital variables using regression analyses, and change over time was considered.

Results—In 6348 eligible patients with known treatment delays, median DNT was 42 minutes and kept decreasing steeply every year (P<0.001). Median DNT of 55 minutes was observed in patients with ODT ≤30 minutes, whereas it declined for patients presenting within the last 30 minutes of the 3-hour time window (median, 33 minutes) and of the 4.5-hour time window (20 minutes). For ODT within the first 30 minutes of the extended time window (181–210 minutes), DNT increased to 42 minutes. DNT was stable for ODT for 30 to 150 minutes (40–45 minutes). We found a weak inverse overall correlation between ODT and DNT (R^2=−0.12; P<0.001), but it was strong in patients treated between 3 and 4.5 hours (R^2=−0.75; P<0.001). ODT was independently inversely associated with DNT (P<0.001) in regression analysis. Octogenarians and women tended to have longer DNT.

Conclusions—DNT was decreasing steeply over the last years in dedicated stroke centers; however, significant oscillations of in-hospital treatment delays occurred at both ends of the time window. This suggests that further improvements can be achieved, particularly in the elderly. **(*Stroke*. 2013;44:2808-2813.)**

Key Words: door-to-needle time ■ emergencies ■ ischemic stroke ■ outcome ■ thrombolysis

It is widely recognized that, in acute stroke, time is brain[1] and that the earlier intravenous thrombolysis (IVT) treatment is administered, the better the outcome.[2–4] Remarkably, inverse relationship between onset-to-door time (ODT) and door-to-needle time (DNT) in stroke thrombolysis was previously addressed.[5–11] According to these reports, every 10-minute raise in ODT increases the likelihood of receiving IVT within 60 minutes from hospital admission (DNT) by ≈20%. These data come from nation-wide stroke unit registries,[6] nation-wide general stroke population registries,[9–11] and from International Stroke Thrombolysis Registries (ISTR),[12] including centers with different levels of expertise in acute stroke care.

In this study, it was our intention to analyze the relationship between ODT and DNT in 10 dedicated stroke centers with a long tradition of acute stroke care, high volume of patients, and a proven track record of participating in acute stroke

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trials. Particularly, we explored whether DNTs are shortening steeper than elsewhere and whether dedicated stroke centers can abolish the inverse relationship between ODT and DNT.

Patients and Methods

Study Setting

This observational study is a joint project of 10 European stroke centers. The study was approved by the relevant authorities in each participating center if required. This study was approved in the coordinating center (Helsinki) as a registry but did not require ethical board review.

Data from individual consecutive patients were collected with a standardized form with predefined variables. Local study investigators filled in the forms systematically using prospectively ascertained in-hospital thrombolysis registries. Completed forms from all centers were compiled in the coordinating center Helsinki, where the analyses of the pooled data were performed. The following prospectively ascertained variables were used: age, sex, onset-to-treatment time (OTT), ODT, DNT, year of admission, baseline stroke severity evaluated by the National Institutes of Health Stroke Scale (NIHSS) score, vascular risk factors according to predefined criteria,[13] and stroke mechanism according to the Trial of Org 10172 in Acute Stroke Treatment criteria.[14] All medical conditions refer to condition before index stroke. The baseline cohort comprised 7106 patients treated with IVT (Table 1), of whom we excluded patients who received IVT >5 hours from symptom onset (n=369), patients with unknown treatment delays (n=324), and patients with in-hospital stroke (n=65). Hence, 6348 patients were eligible for the final analysis. Patients receiving intra-arterial or bridging therapies have not been included in the database.

The primary analysis was the relationship between ODT and DNT. Secondarily, we analyzed treatment delays according to sex, age, and baseline NIHSS. We also calculated DNT changes over years. Nearly all (>98%) patients were evaluated by examiners certified in NIHSS (video training in NIHSS).

Statistical Analyses

After data pooling, distribution was tested. Because of non-normal distribution of all treatment delays, age, and NIHSS, data are presented as median and interquartile range (IQR). Groups were compared with the independent samples Mann–Whitney *U* or Kruskal–Wallis tests, as appropriate. Correlations were tested with Spearman test. A model of linear regression was constructed with DNT (continuous data) as dependent parameter. The model included age, baseline NIHSS, sex, ODT by categories of 30 minutes, year of admission, and center. Condition index of eigenvalue was used to test multicollinearity (ie, a high degree of correlation among several independent variables). This commonly occurs in regression models with a large number of independent variables; some of them may measure the same phenomena. Because of multicollinearity, even small changes in the data produce wide changes in the parameter estimates, coefficients may have very high SE and low significance levels, and coefficients may have the incorrect sign or implausible magnitude. Values of condition index >15 were considered as having a possible problem with collinearity, whereas those with >30 as serious problem. Statistical significance was set at 0.05 (2-tailed). Analyses were performed on IBM SPSS 18 (IBM Corp; Armonk, NY).

Results

We observed a robust annual decrease of DNT (Figure 1A–1C). Median DNT in the pooled cohort was 42 minutes (IQR, 26–65), and >80% of all patients were treated within 3 hours from symptom onset. The rest of the baseline characteristics are shown in Table 2.

When analyzing DNT in 30-minute categories of ODT (Table 3), we observed the highest DNT in patients presenting within 30 minutes from symptom onset (median, 55 minutes; IQR, 35–75). Thereafter, DNT decreased and remained similar (median, 40–45 minutes) for ODT between 30 and 150 minutes, whereafter it decreased to a median of 33 minutes (IQR, 20–58) for patients admitted within the last 30 minutes of the 3-hour time window. In the first 30 minutes (ODT 181–210 minutes) of the extended time, window DNT rose back to a median of 42 minutes (IQR, 28–60) but decreased to 20 minutes (IQR, 14–28) for patients presenting within the last 30 minutes of the 4.5-hour time window. There was no significant difference in mortality and frequencies of symptomatic intracranial hemorrhage among the patients admitted close to the end of the time windows (3-hour and 4.5-hour, before and after European Cooperative Acute Stroke Study [ECASS]-III publication, respectively) compared with other ODT categories (data not shown).

Secondary analysis of DNT versus ODT was performed in strata of age, baseline NIHSS, and sex. Compared with moderate stroke severity (NIHSS 7–12), patients with mild (NIHSS 0–6) and severe (NIHSS >12) symptoms were treated slower when admitted within 30 minutes from symptom onset (P=0.03), whereas no other changes in DNT occurred (Table 3). Overall, patients older than 50 years of age had somewhat lower DNT than those younger than 50 years of age, but there was no difference in DNT delays in any ODT category among these

Table 1. Contribution of Individual Centers and Basic Baseline Patient Characteristics

Center	Country	n (%)	Age, y	Baseline NIHSS	OTT, min	DNT, min
Barcelona	Spain	226 (3.2)	77 (67–83)	7 (4–13)	139 (100–186)	54 (43–66)
Basel	Switzerland	588 (8.3)	74 (61–81)	12 (8–17)	160 (135–195)	76 (59–99)
Bern	Switzerland	307 (4.3)	70 (62–78)	7 (5–12)	180 (150–220)	85 (65–105)
Erlangen	Germany	820 (11.5)	74 (65–82)	10 (5–15)	120 (90–180)	33 (23–50)
Heidelberg	Germany	1270 (17.9)	74 (66–81)	11 (7–17)	135 (105–180)	45 (30–62)
Helsinki	Finland	1836 (25.8)	69 (60–77)	8 (5–14)	118 (86–160)	26 (17–48)
Lausanne	Switzerland	437 (6.1)	69 (58–78)	13 (8–19)	150 (110–180)	48 (35–65)
Lille	France	591 (8.3)	71 (58–80)	12 (7–17)	148 (116–185)	55 (40–70)
St. Gallen	Switzerland	164 (2.3)	74 (63–81)	8 (4–13)	160 (127–193)	60 (50–80)
Tampere	Finland	867 (12.2)	71 (61–79)	8 (5–14)	128 (100–160)	42 (26–60)

Data are presented as median (interquartile range). DNT indicates door-to-needle time; NIHSS, National Institutes of Health Stroke Scale; and OTT, onset-to-treatment time.

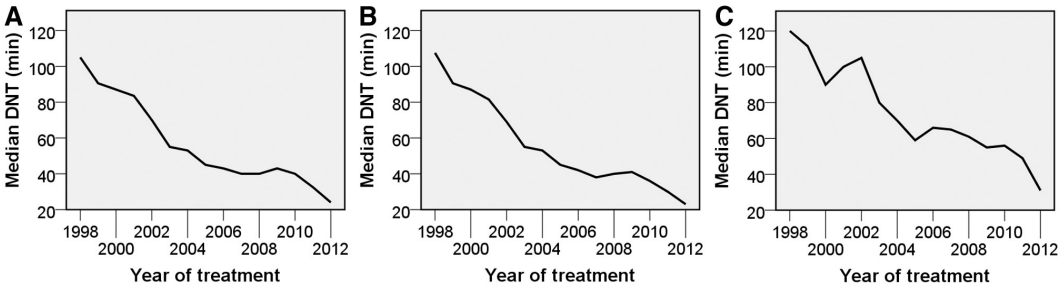

Figure 1. Annual changes in door-to-needle time (DNT). **A**, Patients treated within 4.5 hours from symptom onset. **B**, Patients treated within 3 hours from symptom onset. **C**, Patients treated between 3 and 4.5 hours from symptom onset. There is a remarkable change in DNT per year of treatment in **C**, which is caused by ≥2 factors. **C** represents patients treated between 3 and 4.5 hours from symptom onset (ie, off-label before publication of European Cooperative Acute Stroke Study [ECASS]-III results [end of September 2008]). This means that the number of patients treated within this time window before ECASS-III was rather low (n=299), and even small changes could have caused larger changes. In addition, it shows that centers were performing off-label thrombolysis according to their own (varying) institutional standards. The European Medicines Agency granted conditional license for IV thrombolysis in 2002, when new centers started to deliver the thrombolysis, delays of which were longer in the beginning (effect of experience).

patients. Significantly longer DNT delays were observed for octogenarian patients (Table 4). Women were treated in a generally somewhat slower manner than men, and we observed a significant difference for sex-related delays in patients admitted between 121 and 150 minutes from symptom onset (P<0.01; Table 4). Overall, women were significantly (P<0.001) older than men median 75 (64–82) versus 70 (60–78).

In the whole cohort, we observed a significant but weak inverse correlation between ODT and DNT (R^2=–0.12; P<0.001; Figure 2A). This was similar to the situation in patients treated within 3 hours (R^2=–0.19; P<0.001; Figure 2B); however, there was a strong inverse correlation in patients treated between 3 and 4.5 hours (R^2=– 0.75; P<0.001; Figure 2C). In linear regression analysis, we found an inverse association of ODT (nine 30-minute categories) with DNT: B regression coefficient of −2.95 (−3.48 to −2.41; P<0.001). Age (continuous and octogenarians), baseline NIHSS, and sex were not associated with DNT (P=0.90 [0.14], 0.45, and 0.10, respectively). Belonging to a certain center was also associated with DNT (<0.001); however, a possible collinearity was noted (condition index of eigenvalue, 16.6). Year of treatment had very strong collinearity (condition index of eigenvalue >2500) and was excluded from the model.

Table 2. Demographics and Baseline Characteristics

Parameter	N=6348
Age, y	72 (61–79)
Women, n (%)	2920 (46.0)
Baseline NIH Stroke Scale, score	10 (6–15)
Onset-to-treatment time, min	135 (101–173)
Onset-to-door time, min	80 (59–116)
Door-to-needle time, min	42 (26–65)
Treated within 3 h, n (%)	5199 (81.9)
Treated before publication of ECASS-III, n (%)	3072 (48.4)
Medical history, n (%)	
Diabetes mellitus	1244 (19.6)
Previous stroke	952 (15.0)
Coronary heart disease	1244 (19.6)
Atrial fibrillation	1885 (29.7)
Hypertension	4405 (69.4)
Dyslipidemia	2546 (40.1)
Etiology, n (%)	
Large artery	1047 (16.5)
Cardioembolism	2825 (44.5)
Small vessel disease	413 (6.5)
Other determined	229 (3.6)
Unknown, multiple, not studied	1835 (28.9)

Continuous data are presented as median (interquartile range). DNT indicates door-to-needle time; ECASS-III, European Cooperative Acute Stroke Study-III; NIH, National Institutes of Health; and OTT, onset-to-treatment time.

Post–ECASS-III Aspects

In a population of patients treated with IVT within 3 hours from symptom onset, DNT decreased from a median of 45 minutes (29–66) before ECASS-III to 35 minutes (21–54) thereafter (P<0.001). In the case of patients with OTT 3 to 4.5 hours, DNT was reduced from a median of 70 (39–104) to 54 minutes (32–85; P<0.001). Both before and after the ECASS-III publication, patients with an OTT of 3 to 4.5 hours were treated with larger delays compared with an OTT of <3 hours (P<0.001).

Discussion

Concerns were raised about acute stroke care and treatment decisions because several studies reported faster administration of IVT to patients who present later, whereas physicians wait much longer with their treatment decision in patients presenting very early.[5–11] In other words, the decision takes time when we have time. Such phenomenon is not specific for thrombolysis, neurology, or for medicine. This is a general rule that is known under the term Parkinson's Law (see *The Economist*, November 19, 1955). In the current study, we looked at treatment delays in a pooled cohort of 6348 patients from 10 dedicated stroke centers, where we observed a continuous robust annual decrease (Figure 1) but also found an inverse, though weak, correlation between ODT and DNT. Most significant changes of DNT occurred in the first 30 minutes from symptom onset and in the last 30 minutes of the 3-hour and of the extended time window (Table 3).

The oscillations in DNT observed in our pooled cohort are far away from those reported in the Safe Implementation of Thrombolysis in Stroke (SITS-ISTR),[12] in which DNT

Table 3. Door-to-Needle Time According to Onset-to-Treatment Time Analyzed for the Whole Cohort and Per Baseline Stroke Severity

	Whole Cohort		Tertiles of Baseline NIH Stroke Scale			
ODT	Median DNT, min	Mean DNT, min	0 to 6	7 to 12	>12	*P* Value
Whole ODT range	42 (26–65)	49±30	42 (26–63)	41 (25–65)	44 (27–65)	0.15
≤30 min (n=220)	55 (35–75)	61±36	51 (33–71)	42 (30–75)	59 (42–78)	0.03
31 to 60 min (n=1627)	44 (26–71)	53±35	43 (27–70)	44 (26–73)	44 (26–70)	0.88
61 to 90 min (n=1903)	45 (27–68)	50±31	45 (25–69)	43 (26–67)	45 (28–67)	0.67
91 to 120 min (n=1173)	44 (27–61)	47±27	44 (28–63)	43 (25–60)	44 (27–60)	0.68
121 to 150 min (n=671)	40 (26–55)	44±25	37 (26–55)	41 (27–56)	40 (25–55)	0.79
151 to 180 min (n=378)	33 (20–58)	41±26	36 (20–58)	33 (21–65)	32 (20–50)	0.65
181 to 210 min (n=196)	42 (28–60)	45±23	44 (29–60)	40 (25–58)	42 (29–60)	0.95
211 to 240 min (n=127)	32 (21–45)	36±19	30 (20–47)	30 (22–46)	35 (29–45)	0.43
240 to 270 min* (n=53)	20 (14–28)	22±11	20 (14–28)	20 (9–32)	22 (16–29)	0.43

Data for the whole cohort are presented as median (IQR) and average±SD and as median (IQR) for subgroups of NIH Stroke Scale. *P* values refer to comparison of DNT delays in patients with different baseline stroke severity (NIH Stroke Scale tertiles) per ODT category. DNT indicates door-to-needle time; IQR, interquartile range; NIH, National Institutes of Health; and ODT, onset-to-door time.

*Includes 2 patients with ODT between 270 and 300 minutes.

was larger by an average of 61 minutes in patients with an ODT <30 minutes compared with those presenting in the last 30 minutes of the time window. In our analysis, the corresponding delay in average DNT was 20 minutes in the 3-hour time window and 38 minutes for the extended time window. Given that ≈10% of patients were treated between 3 and 4.5 hours in that SITS-ISTR report, our average 20-minute delay corresponds roughly to a 61-minute delay in the SITS-ISTR. Furthermore, there was virtually no difference (average of 3.5 minutes) in the delays of our patients presenting just before the 3-hour time window and those presenting just after, whereas the corresponding number in SITS-ISTR was 21 minutes.

It was estimated that every 10-minute increase in ODT corresponds to ≈20% higher odds of the DNT being <60 minutes.[6,8,9] Fluctuations in treatment delays were also reported in helicopter emergency transports,[15] in which patients transferred directly to the thrombolysis-administering hospital had a median ODT of 90 (60–125) and a DNT of 45 (30–60) minutes; for patients transferred via another hospital, these delays were 175 (105–257) and 30 (10–68) minutes, respectively. A relieving and important finding in our analysis is that DNT remained similar (Table 3) in patients presenting between 30 and 150 minutes and between 181 and 210 minutes, and oscillations actually occurred at both ends of the time window. Higher delays for ultrarapidly presenting patients can perhaps be explained by insufficient time available to prenotify the stroke center. Indeed, lack of prenotification was shown to negatively influence DNT.[16] In addition, it is more challenging to go through electronic medical chart records in such patients.[17] On the other hand, the very short DNT of 20 minutes in the latest time window segment shows the potential of improving DNT also in the other ODT segments.

In secondary analysis, patients with mild and most severe symptoms were treated slower than other patients when admitted within 30 minutes from symptom onset, but not at later admission time-points. Other than a chance finding, this can, perhaps, be explained by the generally bad condition of those with severe symptoms on early arrival, which is probably more

Table 4. Door-to-Needle Time According to Onset-to-Treatment Time by Sex and Age

ODT (min)	Men (n=3404)	Women (n=2944)	*P* Value	≤50 y (n=624)	>50 y (n=5724)	*P* Value	≤80 y (n=4961)	>80 y (n=1387)	*P* Value
Whole ODT range	41 (25–64)	45 (27–65)	0.01	45 (28–67)	42 (26–65)	0.03	41 (25–64)	45 (30–66)	<0.001
≤30 min (n=220)	52 (33–75)	57 (36–76)	0.26	53 (34–82)	55 (35–75)	0.69	55 (33–80)	54 (39–68)	0.95
31 to 60 min (n=1627)	43 (25–68)	45 (28–76)	0.11	45 (30–69)	43 (26–71)	0.36	44 (26–71)	44 (27–70)	0.80
61 to 90 min (n=1903)	43 (25–68)	45 (28–66)	0.27	47 (25–75)	44 (27–67)	0.20	43 (25–67)	48 (30–68)	0.02
91 to 120 min (n=1173)	42 (27–61)	45 (27–63)	0.25	49 (28–65)	43 (27–60)	0.16	42 (26–60)	46 (30–64)	0.04
121 to 150 min (n=671)	36 (26–54)	42 (30–59)	<0.01	42 (29–52)	40 (26–56)	0.77	37 (25–52)	45 (31–64)	<0.01
151 to 180 min (n=378)	34 (20–59)	32 (20–56)	0.63	27 (18–52)	33 (21–58)	0.38	32 (20–56)	44 (25–66)	0.02
181 to 210 min (n=196)	41 (26–60)	44 (28–60)	0.97	50 (34–77)	41 (27–60)	0.23	43 (26–60)	41 (29–60)	0.94
211 to 240 min (n=127)	32 (21–41)	33 (22–50)	0.78	35 (19–43)	32 (21–46)	0.91	31 (20–45)	35 (24–50)	0.38
240 to 270 min* (n=53)	20 (14–28)	21 (15–30)	0.82	28 (15–48)	20 (14–27)	0.36	20 (14–28)	21 (18–35)	0.81

Data are presented as median (interquartile range). *P* values refer to comparison of door-to-needle delays in women/men or younger/older patients per ODT category. ODT indicates onset-to-door time.

*Includes 2 patients with ODT between 270 and 300 minutes.

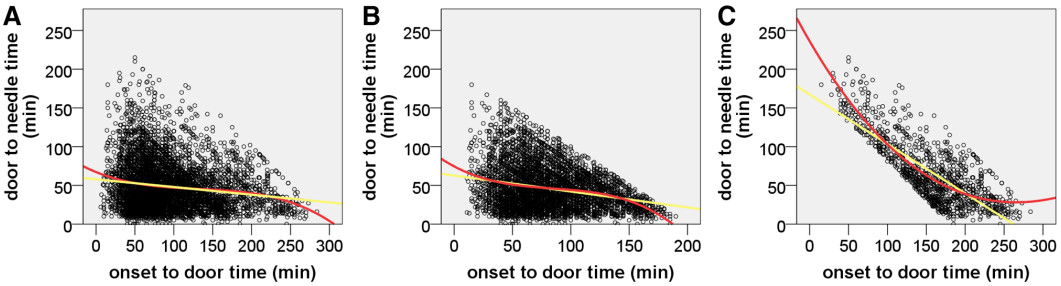

Figure 2. Correlation between onset-to-door and door-to-needle times. The yellow line represents linear correlation, whereas the red line is a cubic function. **A**, Patients treated within 4.5 hours from symptom onset. **B**, Patients treated within 3 hours from symptom onset. **C**, Patients treated between 3 and 4.5 hours from symptom onset.

stabilized at later time-points. Patients with mild symptoms may have longer treatment delays because of waiting for results of advanced imaging or wait-and-see approach. Although in-hospital delays were more stable in octogenarian patients, they were longer compared with younger patients, reflecting perhaps uncertainty of benefit in some centers (Table 4). Result of International Stroke Trial-3[18] will probably change the delays in both octogenarians and those with mild symptoms in the future. We must admit that it can be more time-consuming to obtain all the necessary information (eg, anamnesis, comorbidity) in the elderly, and frequent lack of a partner to provide information is another obstacle. Our observation of tendency toward longer delays in women patients can be explained by their older age compared with men. For the same reason, they also have a higher likelihood of having older partners (compared with men stroke patients) or being widows, both of which negatively influence rapid prenotification and obtaining anamnesis. Nonetheless, age, NIHSS, and sex were not associated with DNT in regression analysis but were associated with ODT. There was a significant effect of the treating center, although possible collinearity was detected.

We observed an inverse correlation between ODT and DNT, but it was a rather weak correlation for the whole cohort and for patients treated in the 3-hour time window. It was actually mostly explained by treatment delays in patients who received IVT between 3 and 4.5 hours. Both SITS-ISTR[12] and Get With The Guidelines Stroke database[9] reported longer DNT for patients treated between 3 and 4.5 hours compared with 0 and 3 hours. This was also the case in our study. What makes the situation different is that there was no change in median DNT in SITS-ISTR after publication of the ECASS III,[19] and only modest changes were reported by Get With The Guidelines Stroke database investigators: median DNT in patients treated within 3 hours decreased from 79 to 74 minutes and in patients treated within 4.5 hours from median 80 to 76 minutes. In our analysis, the corresponding numbers were reduction from median 45 (29–66) to 35 minutes (21–54) and from 70 (39–104) to 54 minutes (32–85).

Our study has limitations. Even if it was not the aim of this study, we do not know how many patients have not received IVT because of late arrivals. But we can at least assume that some of the patients could not have been treated within the 3-hour time window because of a contraindication that could not have been solved before the end of the time window (eg, high blood pressure, lack of information in aphasic patients, needing contact with family). Nowadays, with a longer time window, many of these patients can be given IVT because we have more time to overcome these pitfalls (eg, blood pressure can be lowered). This inevitably leads to increased DNTs because it takes additional time. Only 4.5% of patients were excluded because of the missing treatment delays, and these data would probably not change the results. Another 5% of patients treated >4.5 hours from symptom onset are off-label patients; only 2 of them were treated between 4.5 and 5 hours from symptom onset. This means that the majority of off-label decisions were done at much later time-points, mostly in Heidelberg and Erlangen centers, which deliver off-label thrombolysis based on, for example, MRI mismatch selection.

In conclusion, we found lower DNT when less time was available for thrombolysis, a finding that was particularly pronounced at the very extremes of the thrombolysis time window. Clearly, there is still room for improving DNT, in particular for rapidly presenting patients. Of utmost importance, a continuous robust decrease in DNT over the years was observed, showing the importance and effects of targeted prehospital and emergency room measures to reduce DNT.[17,20]

Disclosures

None.

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