Thrombolytic Therapy in Acute Ischemic Stroke: "Time is Brain"-How to Move the Needle on Door-to-Needle

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Disclosures

- The presenters have no conflicts of interest to disclose

Learning Objectives

At then end of this session, participants should be able to:

1. List the current inclusion and exclusion criteria for intravenous tissue plasminogen activator (tPA) utilization in acute ischemic stroke according to current American Heart Association and the American Stroke Association guidelines
2. Discuss relevant clinical information for dosing and administering tPA in acute ischemic stroke
3. Describe strategies implemented to decrease the door-to-needle time to the goal of less than 60 minutes upon arrival in the Emergency Department

AIS Patient Story-HCA

Guidelines for Acute Ischemic Stroke (AIS)-A Concise Review

Guidelines for AIS-A Concise Review

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

Jauch EC, Saver JL, Adams HP, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW, Qureshi AI, et al. Guidelines for the early management of patients with acute ischemic stroke-a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2013; 44: 870-947.

Guidelines for AIS-A Concise Review

- ED patients with suspected acute ischemic stroke should be triaged with same priority as patients with AMI, trauma, regardless of the severity of neurological deficits

Table 5. ED-Based Care

Action	Time
Door to physician	≤10 minutes
Door to stroke team	≤15 minutes
Door to CT initiation	≤25 minutes
Door to CT interpretation	≤45 minutes
Door to drug (≥80% compliance)	≤60 minutes
Door to stroke unit admission	≤3 hours

CT indicates computed tomography; and ED, emergency department.
Source: Bock.[96]

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- Emergency imaging of the brain is recommended BEFORE initiating any specific therapy to treat AIS
- Non-contrast-enhanced computed tomography (NECT) or MRI is recommended BEFORE IV tPA to exclude intracranial hemorrhage
- Imaging should be interpreted within 45 minutes of patient arrival in the ED by a physician with expertise in reading
- IV tPA is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of extent

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Guidelines for AIS-A Concise Review

- Patients who have elevated blood pressure and are otherwise eligible for treatment with tPA, should have blood pressure carefully lowered to <185mmHg (SBP) and <110mmHg (DBP) BEFORE fibrinolytic therapy is started
- If patient is given medications to lower BP, clinician should ensure that BP is stabilized at the lower level before beginning tPA and for at least the first 24h after tPA

Table 9. Potential Approaches to Arterial Hypertension in Acute Ischemic Stroke Patients Who Are Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:
Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time; or
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate
If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA
Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:
Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:
Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or
Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

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Guidelines for AIS-A Concise Review

- Patients eligible for IV tPA, benefit of therapy is time dependent and treatment should be initiated as quickly as possible. Door-to-needle time should be within 60 minutes from ED arrival
- Dose of tPA is 0.9mg/kg, maximum dose 90mg is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke
- Eligible patients can be treated in the time period of 3-4.5 hours after stroke onset; additional exclusion criteria for this group
- Use of tPA in patients that take direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is NOT recommended unless aPTT, INR, platelet count and ECT, TT or appropriate direct factor Xa activity assays are normal, or the patient has NOT received a dose of these agents for >2 days (assuming normal renal function)

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Guidelines for AIS-A Concise Review

Table 10. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

Table 11. Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative exclusion criteria
Aged >80 years
Severe stroke (NIHSS>25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

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Guidelines for AIS-A Concise Review

Table 12. Treatment of Acute Ischemic Stroke: Intravenous Administration of rtPA

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as a bolus over 1 minute.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV rtPA is being administered) and obtain emergent CT scan.
Measure blood pressure and perform neurological assessments every 15 minutes during and after IV rtPA infusion for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV rtPA treatment.
Increase the frequency of blood pressure measurements if systolic blood pressure is >180 mm Hg or if diastolic blood pressure is >105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels (Table 8).
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 hours after IV rtPA before starting anticoagulants or antiplatelet agents.

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Guidelines for AIS-A Concise Review

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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Eric E. Smith, MD, MPH, FAHA; on behalf of the American Heart Association
Stroke Council and Council on Epidemiology and Prevention

Purpose—To critically review and evaluate the science behind individual eligibility criteria (indication/inclusion and contraindications/exclusion criteria) for intravenous recombinant tissue-type plasminogen activator (alteplase) treatment in acute ischemic stroke. This will allow us to better inform stroke providers of quantitative and qualitative risks associated with alteplase administration under selected commonly and uncommonly encountered clinical circumstances and to identify future research priorities concerning these eligibility criteria, which could potentially expand the safe and judicious use of alteplase and improve outcomes after stroke.

Methods—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge and, when appropriate, formulated recommendations using standard American Heart Association criteria. All members of the writing group had the opportunity to comment on and approved the final version of this document. The document underwent extensive American Heart Association internal peer review, Stroke

Demaerschalk BM,Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke-a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581-641.

Guidelines for AIS-A Concise Review

Extended 3-to-4.5 Hour Window-Recommendations:

- tPA is recommended for carefully selected patients who meet criteria and are treated in 3-to-4.5-hour window
- Patients >80 years old presenting in 3-to-4.5-hour window, tPA treatment is safe and can be as effective as in younger patients
- Patients taking warfarin and with INR <1.7 who present in the 3-to-4.5 hour window, tPA appears safe and may be beneficial
- Benefit of tPA for AIS patients with NIHSS score >25 and presenting in the 3-to-4.5-hour window is uncertain
- Patients with diabetes and prior history of stroke, presenting in the 3-to-4.5-hour window, tPA may be as effective as treatment in the 0-to-3-hour window a reasonable option

Demaerschalk BM,Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke-a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581-641.

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Absolute Contraindications-Recommendations:

- In AIS patients with recent severe head trauma (within 3 months), tPA is contraindicated
- tPA is contraindicated in patients presenting with symptoms and signs most consistent with SAH
- tPA is contraindicated for patients with CT revealing acute intracranial hemorrhage
- tPA is contraindicated for patients with BG <50mg/dL
- Safety and efficacy of tPA for AIS patients with platelets <100,000/mm^3, INR>1.7, aPTT>40 seconds or PT 15 seconds is unknown and tPA is NOT recommended

Demaerschalk BM,Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke-a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581-641.

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Not Recommended or Potentially Harmful-Recommendations:

- The use of tPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors within last 48 hours has no been firmly established but may be harmful
- tPA in patients who have received a treatment dose of LMWH within the previous 24 hours is NOT recommended
- tPA in patients who have a history of intracranial hemorrhage is potentially harmful
- Patients with a structural GI malignancy or recent bleeding event within 21 days of AIS should be considered high risk and tPA is considered potentially harmful
- tPA in patients with intra-axial intracranial neoplasm is potentially harmful

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Not Recommended or Potentially Harmful-Recommendations:

- tPA in patients with giant unruptured aneurysm (>10mm) and unsecured intracranial aneurysm is not well established
- Patients presenting with AIS who are known to harbor and unruptured and untreated intracranial vascular malformation, the usefulness and risks of tPA are not well established
- Patients with history of intracranial/spinal surgery within the prior 3 months, tPA is potentially harmful
- Patients with symptoms consistent with infective endocarditis, tPA is not recommended because of the increased risk of ICH
- tPA in patients with known or suspected to be associated with aortic arch dissection is NOT recommended and is potentially harmful

Demaerschalk BM,Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke-a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581-641.

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Conditions that May Require Urgent Consultation Prior to tPA: Recommendations

- tPA may be considered in pregnancy when anticipated benefits of treating moderate to severe stroke outweigh the risks of uterine bleeding; recommend urgent consultation with OB/GYN, perinatologist
- If there is a history of recent or active vaginal bleeding causing clinically significant anemia, urgent consultation with gynecologist is probably indicated before a decision about tPA is made
- For patient with major AIS like to produce severe disability and acute pericarditis, treatment with tPA may be reasonable; urgent consultation with a cardiologist is recommended

Demaerschalk BM,Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke-a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2016; 47:581-641.

Guidelines for AIS-A Concise Review

Inclusion/Exclusion Criteria for ACUTE ISCHEMIC STROKE
IV t-PA – Alteplase/Intra-arterial intervention
Symptom Onset date___ / time___ Time Arrived Hospital: ____
STAT tPA given@ time ____ *(Door to Needle **<60 min**)*

Intravenous (IV) Thrombolysis Inclusion Criteria	Yes
1. Clinical diagnosis of ischemic stroke with measurable neurological deficit presumed due to cerebral ischemia after CT excludes Hemorrhage	
2. Aged 18 years or older	
3. Time of last known well established to be less than 180 minutes (3 Hours)	
4. Time of last known well established to be less than 270 minutes (4.5 hours) and pt does **not** have **any** of the following limiting factors (pg 36/37 removal of > 80yo, anticoagulants regardless of INR, and NIHSS, as well as stroke and DM) • CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)	
Absolute Contraindications: IV tPA (Alteplase) is contraindicated if ANY of the following are present:	Yes
1. Significant Head Trauma in previous 3 months (#2 pg 22)	
2. Symptom suggestive of Subarachnoid Hemorrhage even with normal CT (#1 pg 35)	
3. Current intracranial hemorrhage (#1 pg 15)	
4. Blood glucose concentration <50mg/dL (2.7mmol/L) (#1 pg31)	
5. Acute bleeding diathesis including but not limited to (#1 pg 18) • Platelet count <100,000/mm3 • Current use of anticoagulant with INR >1.7 (#2 pg 20) or PT >15 seconds or PTT>40	
6. **Sustained** elevated blood pressure (systolic >185mmHg or diastolic >110mmHg)	
Not recommended or Potentially Harmful (Recommend Consultation with Neurologist)	**Yes**
7. Use of direct factor Xa inhibitors or direct thrombin inhbitors within last 48 hours (#4 pg 20)	
8. Low Weight Molecular Heparin within the last 24 hours (#3 pg 20)	
9. CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)	
10. History of intracranial hemorrhage (#2 pg 27)	
11. Gastrointestinal malignancy or hemorrhage within last 21 days (#2 pg25)	
12. Intra-axial cranial neoplasm(#2 pg 28), giant aneurysm >10mm(#1,2 pg 27), AVM (#1 pg28)	
13. Recent intracranial or intraspinal surgery in last 3 months (#1 pg 24)	
14. Infective Endocarditis (#1 pg 24)	
15. Aortic Arch Dissection- Consider CV Surgery Consult (#1 pg 39)	
Conditions that may require URGENT consultation prior to alteplase administration	**Yes**
16. Moderate to Severe Stroke with Pregnancy- Consult OB/GYN and discuss risk benefits with patient (#1,3 pg 16)	
17. Recent or Current menorrhagia resulting in anemia- Consult OB/GYN and discuss risk and benefits with patient (#3 pg38)	
18. Pericarditis- Consult Cardiology (#1 pg 23)	
All other conditions are relative and should involve a balanced risk of potential bleeding versus potential disability discussion with the patient and/ or family member	**Yes**
19. Patient or family refused Because stroke is a medical emergency, if patient is not competent and no immediate family is available, it is recommended to proceed with alteplase. (pg 42#1)	

Inclusion Criteria for Endovascular Therapy by Neuro- Interventionalist	**Yes**
• Stroke onset less than 4.5 (up to 6 hours in hospitals with endovascular capability)-Goal to groin puncture 6 hours • No pre-existing disability • NIHSS>6 • ASPECT score6+ or less than <1/3 MCA territory hypodensity or report: "No acute abnormalities" ie: "clean CT" • CTA with ICA, MCA, M1 thrombus	
Patient meets criteria above for endovascular intervention contact in house neurointerventionalist STAT ***If no neurointerventionalist available in house, contact the transfer center immediately and use the term ELVO to get emergency transfer.***	
NAME: DATE: TIME:	

HCA Gulf Coast Division-Inclusion and Exclusion Criteria

HCA | Pharmacy Services

Clinical Pearls for Dosing and Administration of tPA in Acute Ischemic Stroke (AIS)

Clinical Pearls for Dosing and Administration of tPA

Dosing of tPA in Acute Ischemic Stroke:

- The recommended dose of alteplase is 0.9mg/kg IV, with a maximum dose of 90mg
- 10% of the total dose is given as an IV bolus over 1 minute, then give the remainder of the dose over 1 hour

Clinical Pearls for Dosing and Administration of tPA

IV tPA administration:

- tPA should be administered as soon as prepared by pharmacy and orders have been given by the physician
- Blood pressure and neurological assessments should be preformed every 15 minutes during and after the administration of tPA for 2 hours, then every 30 minutes for 6 hours, and then every hour until 24 hours after completion of treatment

Clinical Pearls for Dosing and Administration of tPA

IV tPA administration:

- The frequency of BP monitoring needs to be increased if systolic BP>180 mmHg or if diastolic BP is >105 mm HG. Antihypertensive medications may be used (Labetalol, Cardene) to maintain blood pressure at or below these levels
- If the patient has a worsening neurological examination, develops a severe headache, acute hypertension, nausea or vomiting discontinue the infusion and obtain a stat CT scan

Clinical Pearls for Dosing and Administration of tPA

IV tPA administration:

- A repeat CT or MRI scan should be ordered 24 hours after the completion of tPA prior to starting any anticoagulants or antiplatelets
- Avoid placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters during administration of tPA if patient can be safely managed without them
- Post thrombotic therapy patients are to be admitted to an ICU bed for a minimum of 24 hours following treatment for close monitoring

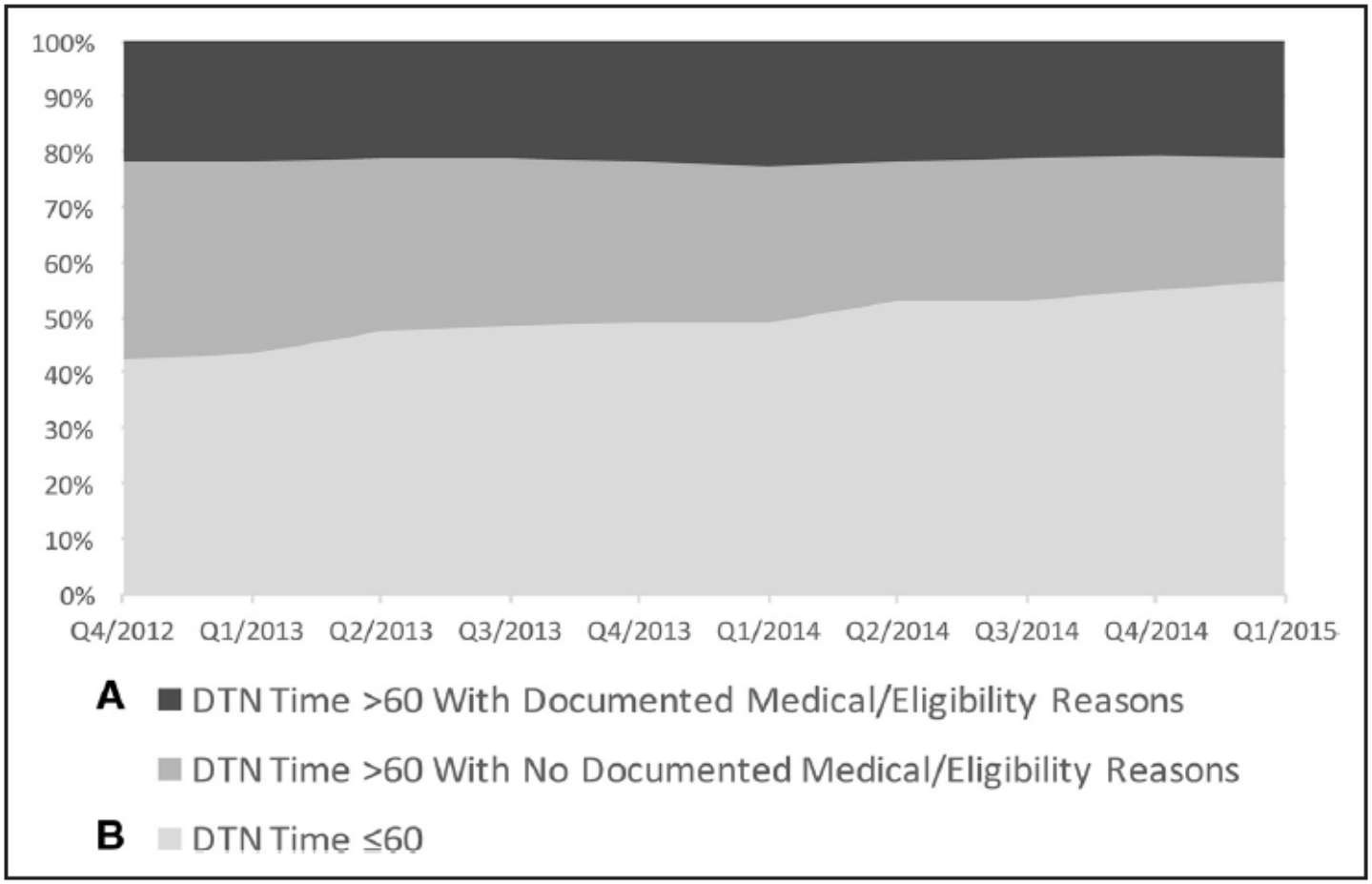
Clinical Pearls for Dosing and Administration of tPA

IV tPA possible complications:

- The most common complication associated with thrombolytic therapy is bleeding
- Bleeding maybe internal or superficial
- Any change in the patients level of consciousness maybe an indication of a hemorrhage
- If an intracerebral hemorrhage is suspected, notify the physician and order coagulation panel and repeat CT without contrast

Strategies to Decrease Door-to-Needle Times in the Acute Care Hospital Setting

Strategies to Decrease Door-to-Needle Times



Kamal N, Sheng S, Xian Y, Matsouaka R, Hill MD, Bhatt DL, Saver JL, Reeves MJ, Fonarow GC, Schwamm LH and Smith EE. Delays in Door-to-Needle Times and Their Impact on Treatment Time and Outcomes in Get With The Guidelines-Stroke. *Stroke.* 2017; 48: 946-954.

Strategies to Decrease Door-to-Needle Times

Table 2. Reasons for Delayed Treatment Among Patients With a DTN Time >60 Minutes (N=27 518)

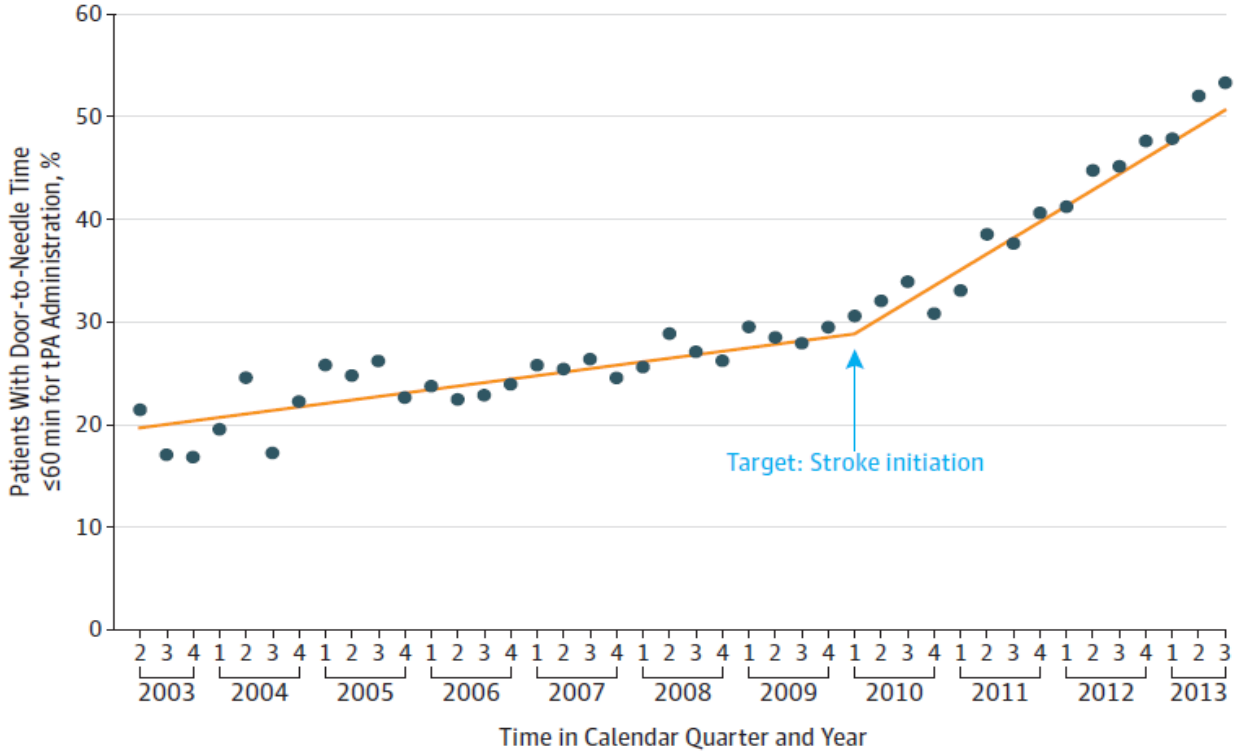
Category	N	%	DTN, Median (IQR), min
DTN ≤60 min			
No reasons for delay recorded	27 778	50.24	47 (38–54)
DTN>60 min			
No reasons for delay recorded	10 086	18.24	79 (69–97)
Eligibility: social/religious	274	0.50	82 (71–100)
Eligibility: initial refusal	1797	3.25	88 (74–111)
Eligibility: care team unable to determine eligibility	5098	9.22	89 (74–112)
Medical: hypertension requiring aggressive control	3936	6.94	84 (71–103)
Medical: further evaluation for hypoglycemia or seizure	977	1.77	95 (77–121)
Medical: management of emergent/acute condition	911	1.65	89 (74–113)
Hospital: delay in stroke diagnosis	573	1.04	92 (77–118)
Hospital: in-hospital delay	3514	6.35	80 (69–97)
Hospital: equipment-related delay	238	0.43	79 (68–94)
Hospital: other	1714	3.10	82 (70–101)
Number of reasons			
No reason for delay recorded	37 864	68.5	52 (41–62)
1 reason for delay recorded	16 003	28.94	84 (71–104)
2 reasons for delay recorded	1362	2.46	93 (76–116)
>2 reasons for delay recorded	67	0.12	95 (76–131)

DTN indicates door-to-needle; and IQR, interquartile range.

Kamal N, Sheng S, Xian Y, Matsouaka R, Hill MD, Bhatt DL, Saver JL, Reeves MJ, Fonarow GC, Schwamm LH and Smith EE. Delays in Door-to-Needle Times and Their Impact on Treatment Time and Outcomes in Get With The Guidelines-Stroke. *Stroke.* 2017; 48: 946-954.

Strategies to Decrease Door-to-Needle Times

Figure 2. Time Trend in the Proportion of Patients with Door-to-Needle Times for Tissue Plasminogen Activator (tPA) of 60 Minutes or Less During the Preintervention and Postintervention Periods of Target: Stroke



Fonarow GC, Zhao X, Smith EE, Saverr JL, Reeves MJ et. al. Door-to-Needle Times for Tissue Plasminogen Activator Administration and Clinical Outcomes in Acute Ischemic Stroke Before and After a Quality Improvement Initiative. *JAMA.* 2014; 311 (16): 1632-1640.

Strategies to Decrease Door-to-Needle Times

Original Investigation

Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke

A Randomized Clinical Trial

Martin Ebinger, MD; Benjamin Winter, MD; Matthias Wendt, MD; Joachim E. Weber, MD; Carolin Waldschmidt, MD; Michal Rozanski, MD; Alexander Kunz, MD; Peter Koch, MD; Philipp A. Kellner, MD; Daniel Gierhake, MD; Kersten Villringer, MD; Jochen B. Fiebach, MD; Ulrike Grittner, PhD; Andreas Hartmann, MD; Bruno-Marcel Mackert, MD; Matthias Endres, MD; Heinrich J. Audebert, MD; for the STEMO Consortium

IMPORTANCE Time to thrombolysis is crucial for outcome in acute ischemic stroke.

OBJECTIVE To determine if starting thrombolysis in a specialized ambulance reduces delays.

DESIGN, SETTING, AND PARTICIPANTS In the Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S), conducted in Berlin, Germany, we randomly assigned weeks with and without availability of the Stroke Emergency Mobile (STEMO) from May 1, 2011, to January 31, 2013. Berlin has an established stroke care infrastructure with 14 stroke units. We included 6182 adult patients (STEMO weeks: 44.3% male, mean [SD] age, 73.9 [15.0] y; control weeks: 45.2% male, mean [SD] age, 74.3 [14.9] y) for whom a stroke dispatch was activated.

INTERVENTIONS The intervention comprised an ambulance (STEMO) equipped with a CT scanner, point-of-care laboratory, and telemedicine connection; a stroke identification algorithm at dispatcher level; and a prehospital stroke team. Thrombolysis was started before transport to hospital if ischemic stroke was confirmed and contraindications excluded.

MAIN OUTCOMES AND MEASURES Primary outcome was alarm-to-thrombolysis time. Secondary outcomes included thrombolysis rate, secondary intracerebral hemorrhage after thrombolysis, and 7-day mortality.

RESULTS Time reduction was assessed in all patients with a stroke dispatch from the entire catchment area in STEMO weeks (3213 patients) vs control weeks (2969 patients) and in patients in whom STEMO was available and deployed (1804 patients) vs control weeks (2969 patients). Compared with thrombolysis during control weeks, there was a reduction of 15 minutes (95% CI, 11-19) in alarm-to-treatment times in the catchment area during STEMO weeks (76.3 min; 95% CI, 73.2-79.3 vs 61.4 min; 95% CI, 58.7-64.0; $P < .001$). Among patients for whom STEMO was deployed, mean alarm-to-treatment time (51.8 min; 95% CI, 49.0-54.6) was shorter by 25 minutes (95% CI, 20-29; $P < .001$) than during control weeks. Thrombolysis rates in ischemic stroke were 29% (310/1070) during STEMO weeks and 33% (200/614) after STEMO deployment vs 21% (220/1041) during control weeks (differences, 8%; 95% CI, 4%-12%; $P < .001$, and 12%, 95% CI, 7%-16%; $P < .001$, respectively). STEMO deployment incurred no increased risk for intracerebral hemorrhage (STEMO deployment: 7/200; conventional care: 22/323; adjusted odds ratio [OR], 0.42, 95% CI, 0.18-1.03; $P = .06$) or 7-day mortality (9/199 vs 15/323; adjusted OR, 0.76; 95% CI, 0.31-1.82; $P = .53$).

CONCLUSIONS AND RELEVANCE Compared with usual care, the use of ambulance-based thrombolysis resulted in decreased time to treatment without an increase in adverse events. Further studies are needed to assess the effects on clinical outcomes.

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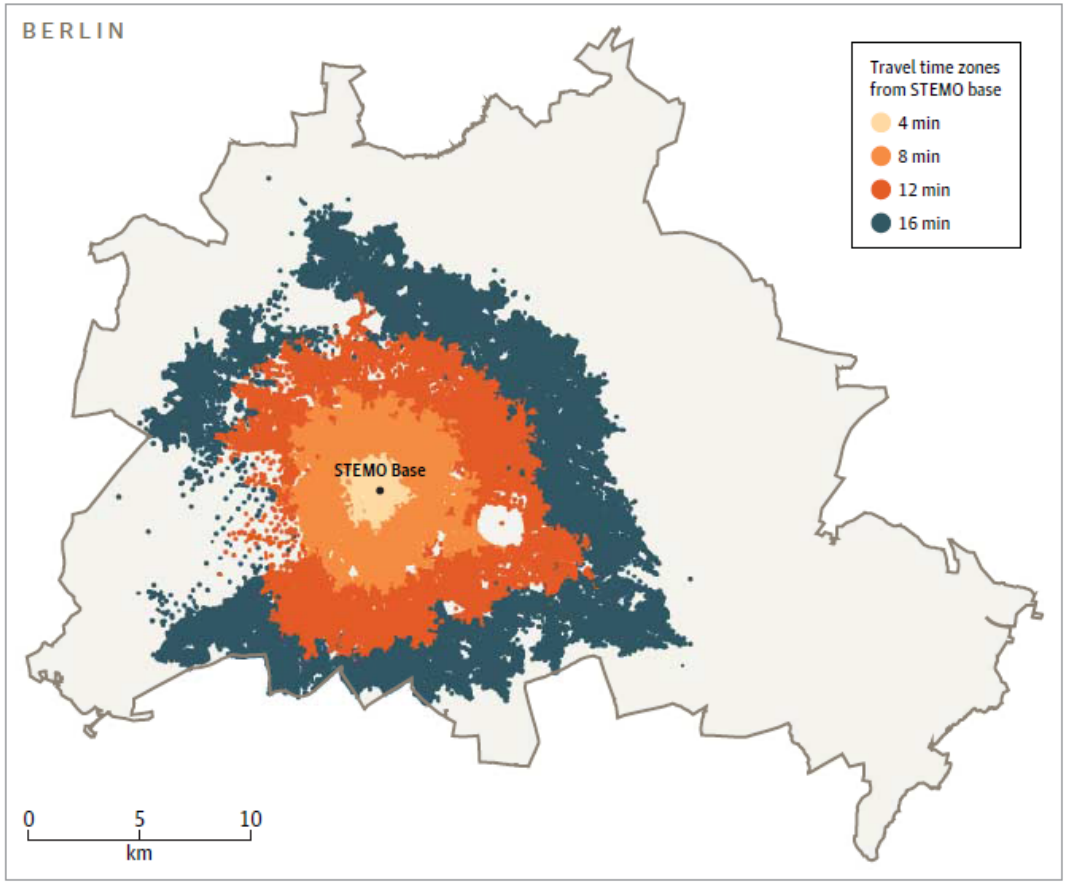
Author Affiliations: Author affiliations are listed at the end of article.

Group Information: The STEMO Consortium members are listed at the end of the article.

Figure 1. Map of Berlin, Germany, With Color-Coded STEMO Catchment Area Around STEMO Base



Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et. Al. The Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke-A Randomized Clinical Trial. *JAMA.* 2014; 311 (16): 1622-1631.

Strategies to Decrease Door-to-Needle Times

Table 2. Outcomes in All Patients and Patients With Ischemic Strokes Receiving Thrombolysis Comparing STEMO Groups With Control Weeks

	Patients With STEMO Deployment	*P* Value[a]	Patients During STEMO Weeks	*P* Value[a]	Patients During Control Weeks
All Patients					
No. of patients	1804		3213		2969
Days in hospital (5 missing), mean (95% CI)	6.4 (6.0-6.7)	.92	6.3 (6.0-6.5)	.89	6.2 (6.0-6.5)
Median (IQR)	5 (0-9)		5 (0-9)		5 (1-9)
In-hospital deaths, No. (%) [95% CI]					
Within 7 d	44 (2.4) [1.8-3.3]	.63	72 (2.2) [1.8-2.8]	.96	66 (2.2) [1.8-2.8]
Total (12 missing)	62 (3.4) [2.7-4.4]	.32	116 (3.6) [3.0-4.3]	.41	119 (4.0) [3.4-4.8]
Patients With Ischemic Stroke Treated With Thrombolysis					
No. of patients	200		310		220
Process indicators					
Days in hospital, mean (95% CI)	9.3 (8.3-10.2)	.37	9.0 (8.3-9.7)	.38	8.9 (7.9-10.0)
Median (IQR)	7 (5-12)		7 (5-11)		7 (5-11)
INR known before start of tPA (1 missing), No. (%) [95% CI]	184 (92.0) [87.4-95.0]	<.001	270 (87.1) [82.9-90.4]	.009	172 (78.5) [72.6-83.5]
Patients treated within 90 min of symptom onset, No. (%) [95% CI]	115 (57.5) [50.6-64.1]	<.001	149 (48.1) [42.6-53.6]	.02	82 (37.4) [31.3-44.0]
Onset-to-treatment time (1 missing), mean (95% CI), min	102.7 (93.9-111.5)	<.001	110.1 (103.4-116.8)	.003	118.5 (111.8-125.2)
Median (IQR), min	81 (56-129)		95 (65-142)		105 (81-145)
Clinical outcomes, No. (%) [95% CI]					
Hemorrhagic complications	7 (3.5) [1.7-7-0]	.18	15 (4.8) [3.0-7.8]	.45	14 (6.4) [3.8-10.4]
In-hospital deaths	14 (7.0) [4.2-11.4]	.79	20 (6.5) [4.2-9.8]	.97	14 (6.4) [3.8-10.4]
Primary safety end point					
Deaths within 7 d (1 missing)	9 (4.5) [2.4-8.4]	.99	14 (4.5) [2.7-7.5]	.99	10 (4.5) [2.5-8.2]
Discharge home, post hoc	87 (43.5) [36.8-50.4]	.39	134 (43.2) [37.8-48.8]	.31	105 (47.7) [41.2-54.3]
Death within 90 d (4 missing)	33 (16.7) [12.1-22.5]	.21	48 (15.6) [12.0-20.1]	.30	27 (12.4) [8.7-17.4]
Times in tPA Treatments at First Assessment[b]					
No. of patients	192		300		218
Hospital door to needle, mean (95% CI), min					42.0 (39.1-44.9)
Median (IQR), min					36 (28-51)
Alarm to hospital arrival, mean (95% CI), min	84.6 (80.8-88.5)	<.001	66.9 (63.2-70.6)	<.001	34.6 (33.5-35.7)
Median (IQR), min	84.5 (72-95)		71 (36-89)		34 (29-40)
Alarm to imaging, mean (95% CI), min	37.7 (35.6-39.7)	<.001	44.0 (42.0-46.0)	<.001	52.4 (50.3-54.4)
Median (IQR), min	35 (30-42)		39 (32-52)		50 (43-59)
Imaging to treatment, mean (95% CI), min	14.1 (12.4-15.8)	<.001	17.4 (15.7-19.0)	<.001	23.8 (21.6-26.1)
Median (IQR), min	12 (7-17)		14 (8-20)		20 (13-31)
Alarm to INR, mean (95% CI), min	30.8 (28.4-33.2)	<.001	40.4 (36.6-44.3)	<.001	74.9 (55.5-94.3)
Median (IQR), min	26 (20-37)		35 (23-50)		48 (39-70)
Alarm to blood cell count, mean (95% CI), min	35.1 (32.1-38.2)	<.001	42.6 (38.7-46.4)	<.001	78.0 (55.4-100.7)
Median (IQR), min	31 (24-41)		37 (27-51)		48 (39-62)
Primary end point					
Alarm to treatment (1 missing), mean (95% CI), min	51.8 (49.0-54.6)	<.001	61.4 (58.7-64.0)	<.001	76.3 (73.2-79.3)
Median (IQR), min	48 (39-56)		55 (44-75)		72 (62-85)

- Study showed ambulance-based thrombolysis was safe, reduced alarm-to-treatment time and increased thrombolysis rates
- Effects need to be weighed against cost of STEMO concept
- Further studies needed to assess the effects on clinical outcomes

Ebinger M, Winter B, Wendt M, Weber JE, Waldschmidt C, Rozanski M, et. Al. The Effect of the Use of Ambulance-Based Thrombolysis on Time to Thrombolysis in Acute Ischemic Stroke-A Randomized Clinical Trial. *JAMA.* 2014; 311 (16): 1622-1631.

Strategies to Decrease Door-to-Needle Times

Table 1 Components of stroke code boot camp
1. NIH Stroke Scale training prior to boot camp
2. Pretest to assess prior knowledge about acute stroke management
3. Lecture on acute stroke code management and imaging
4. Socratic presentation of acute stroke cases
Patient presenting to the ED eligible for IV tPA
Patient presenting to the ED eligible for mechanical thrombectomy
Inpatient stroke code
Patient with contraindications for IV tPA/mechanical thrombectomy
5. Key teaching points included
Symptom discovery vs last known well times
Challenges in history-taking: patients with aphasia, neglect, family members not present
Interpretation of imaging (hemorrhage, large infarct, early infarct signs)
Discussion of indications and contraindications for IV tPA
Criteria for premixing IV tPA
Evaluation for large vessel syndromes
Evidence-based discussion points for risks/benefits of acute therapies for patients/families
Institution-specific protocols
6. Posttest
Abbreviations: ED = emergency department; tPA = tissue plasminogen activator.

Ruff IM, Liberman AL, Caprio FZ, Maas MB, Mendelson SJ, Sorond FA, Bergman D, et al. A resident boot camp for reducing door-to-needle times at academic medical centers. *Neurol Clin Pract*; 2017; 7: 237-245.

Strategies to Decrease Door-to-Needle Times

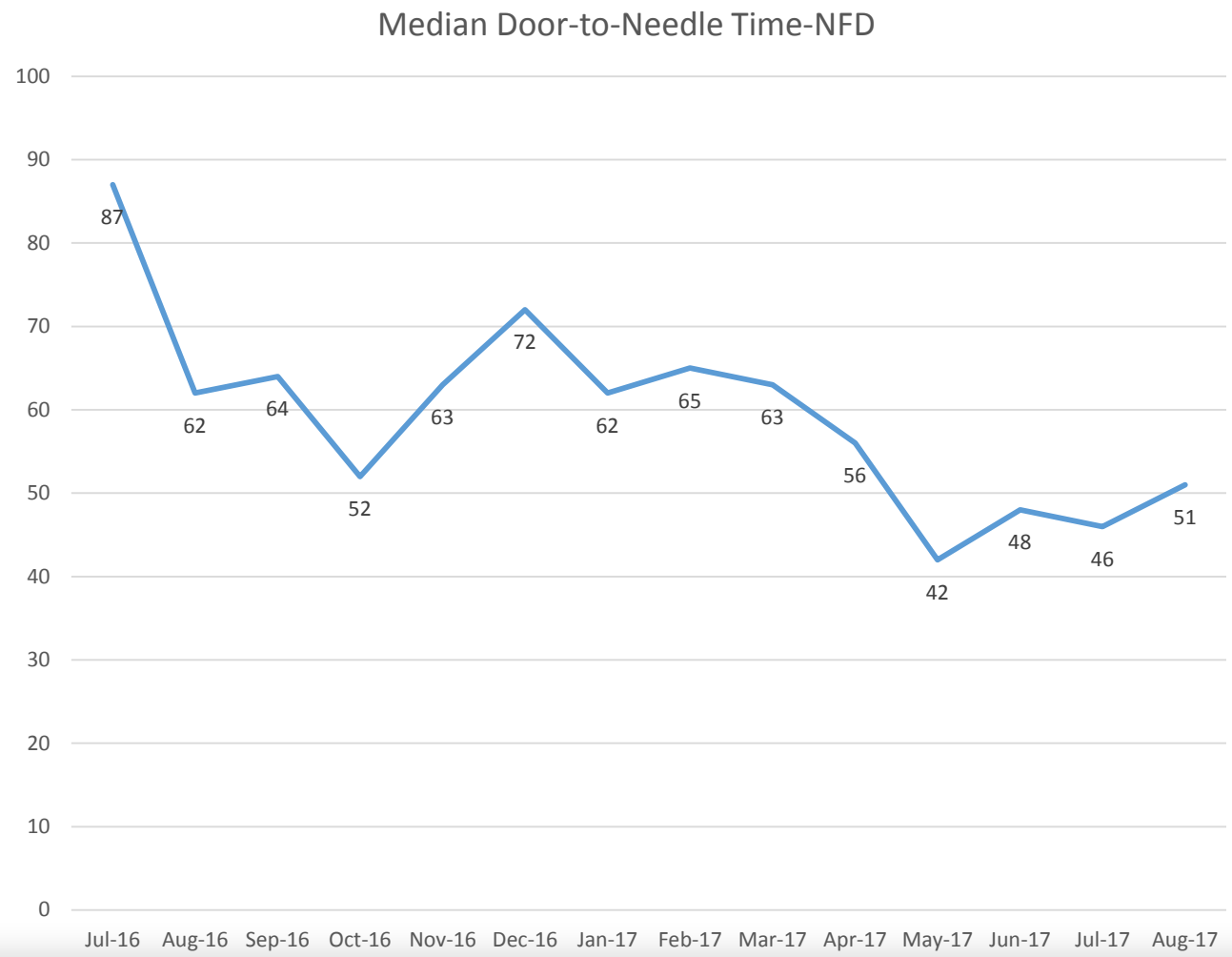
Table 3 Process time-based variables and adverse events for overall population of patients receiving IV tPA

	Overall (n = 170)	Preintervention (n = 72)	Postintervention (n = 98)	*p* Value
Process metrics				
Median (IQR) door-to-stroke code, min	6 (1-17)	6 (0.25-17)	7 (2-17)	0.631
Median (IQR) door-to-CT time, min	18 (11-28)	18 (11-26)	18 (11-31)	0.547
Median (IQR) DTN time, min	67 (46-89)	79 (66-104)	58 (39-72)	0.0001
Median (IQR) onset-to-treatment time, min	132 (105-171)	145 (114-183)	123 (94-157)	0.0001
Median (IQR) onset-to-door time, min	58 (40-88)	54 (39-89)	65 (41-90)	0.693
Median (IQR) stroke code-to-tPA time, min (n = 165, 5 cases with prearrival stroke team activation)	59 (39-75)	75 (64-89)	44 (31-59)	0.0001
DTN time ≤60 min, n (%)	73 (42.9)	13 (18.1)	60 (61.2)	0.0001
Adverse outcomes, n (%)				
Angioedema	2 (1.2)	2 (2.8)	0 (0)	0.178
Any ICH	16 (9.4)	7 (9.7)	9 (9.2)	0.905
Symptomatic ICH	3 (1.8)	3 (4.2)	0 (0)	0.074
Systemic bleeding	10 (5.9)	6 (8.3)	4 (4.1)	0.326
Favorable outcome	143 (83.5)	64 (88.9)	78 (79.6)	0.106
Mimic (adjudicated)	23 (13.5)	5 (6.9)	18 (18.4)	0.031

Abbreviations: DTN = door to needle; ICH = intracerebral haemorrhage; IQR = interquartile range; tPA = tissue plasminogen activator.

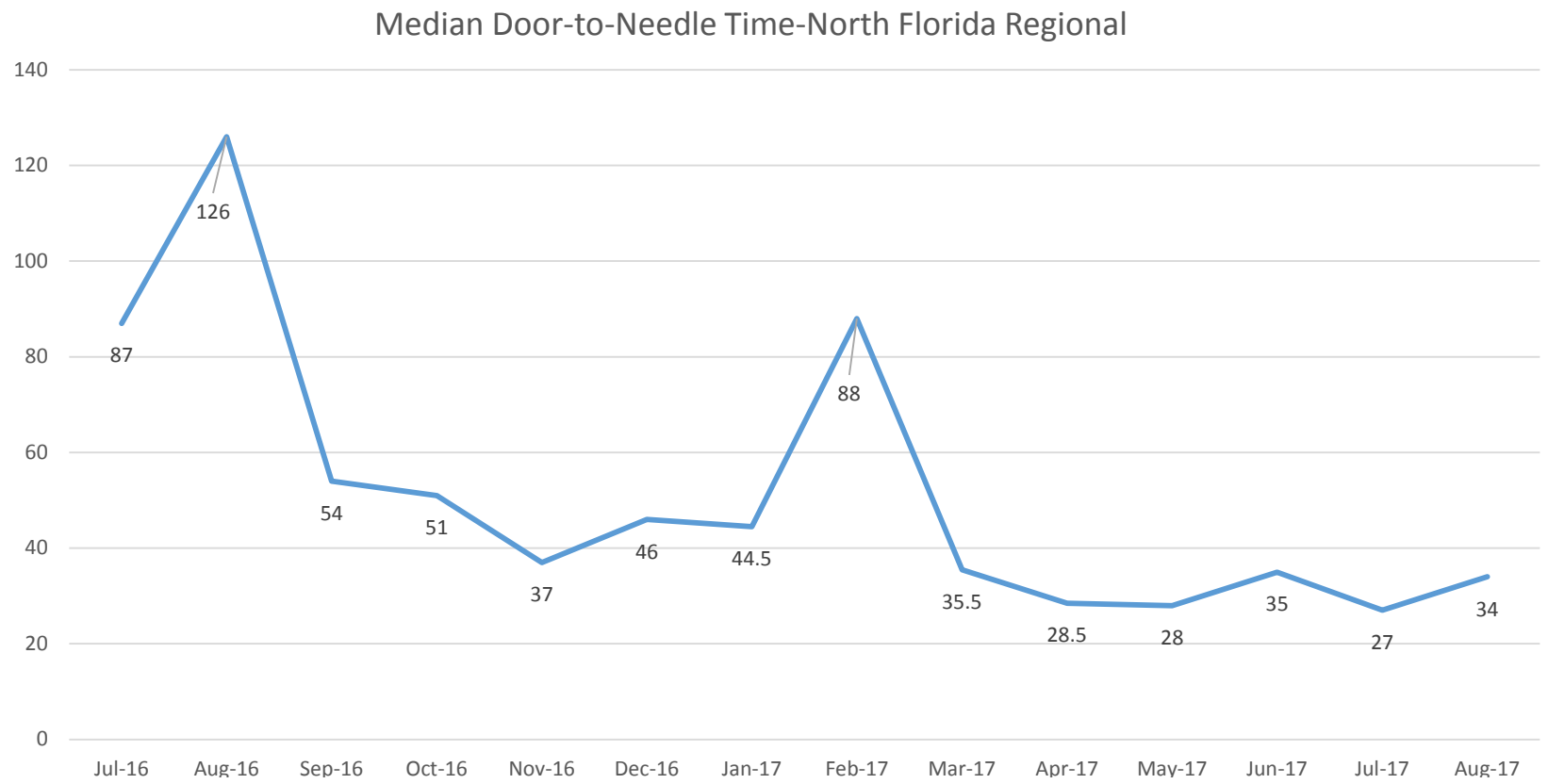
Ruff IM, Liberman AL, Caprio FZ, Maas MB, Mendelson SJ, Sorond FA, Bergman D, et al. A resident boot camp for reducing door-to-needle times at academic medical centers. *Neurol Clin Pract*; 2017; 7: 237-245.

Strategies to Decrease Door-to-Needle Times



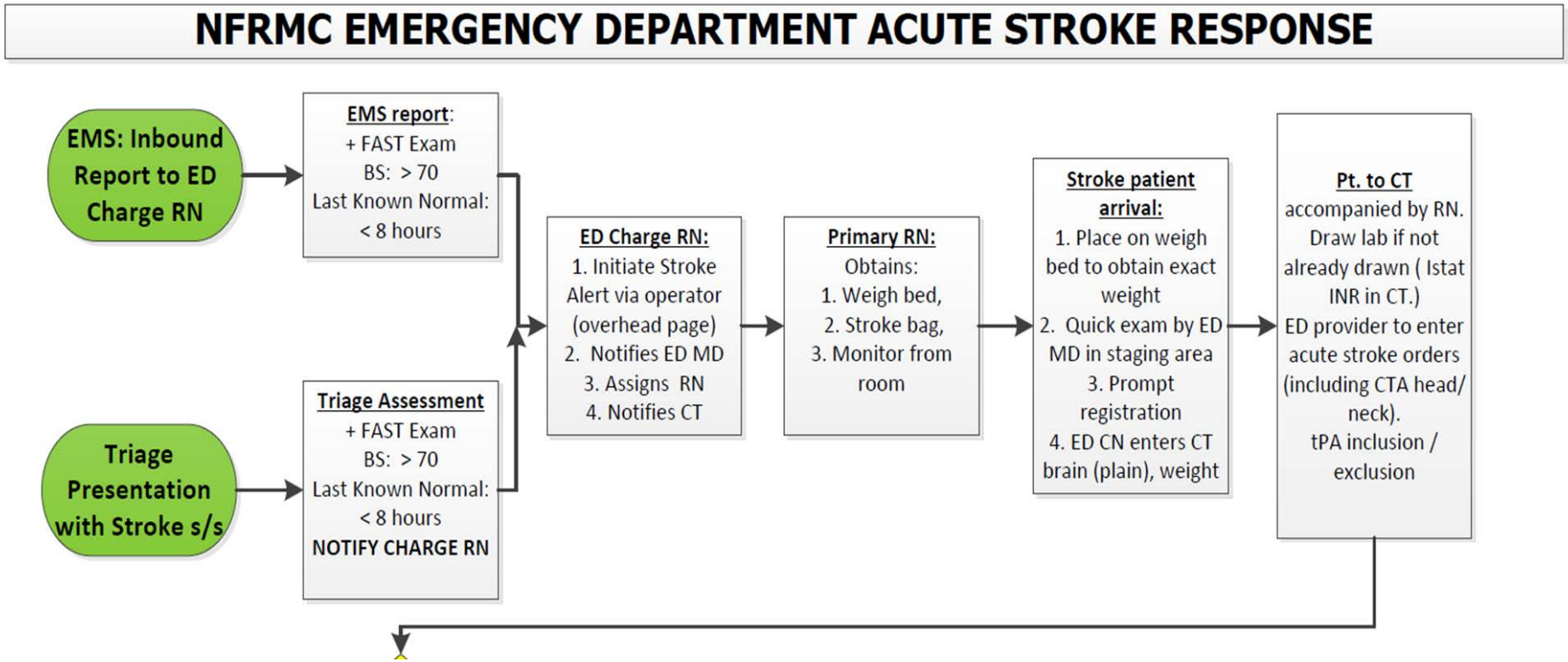
- HCA North Florida Division trend
- Improved overall DTN times by 47%
- From 87 min (July 2016) to 48 min (July 2017)
- Continue to focus on tPA utilization

Strategies to Decrease Door-to-Needle Times



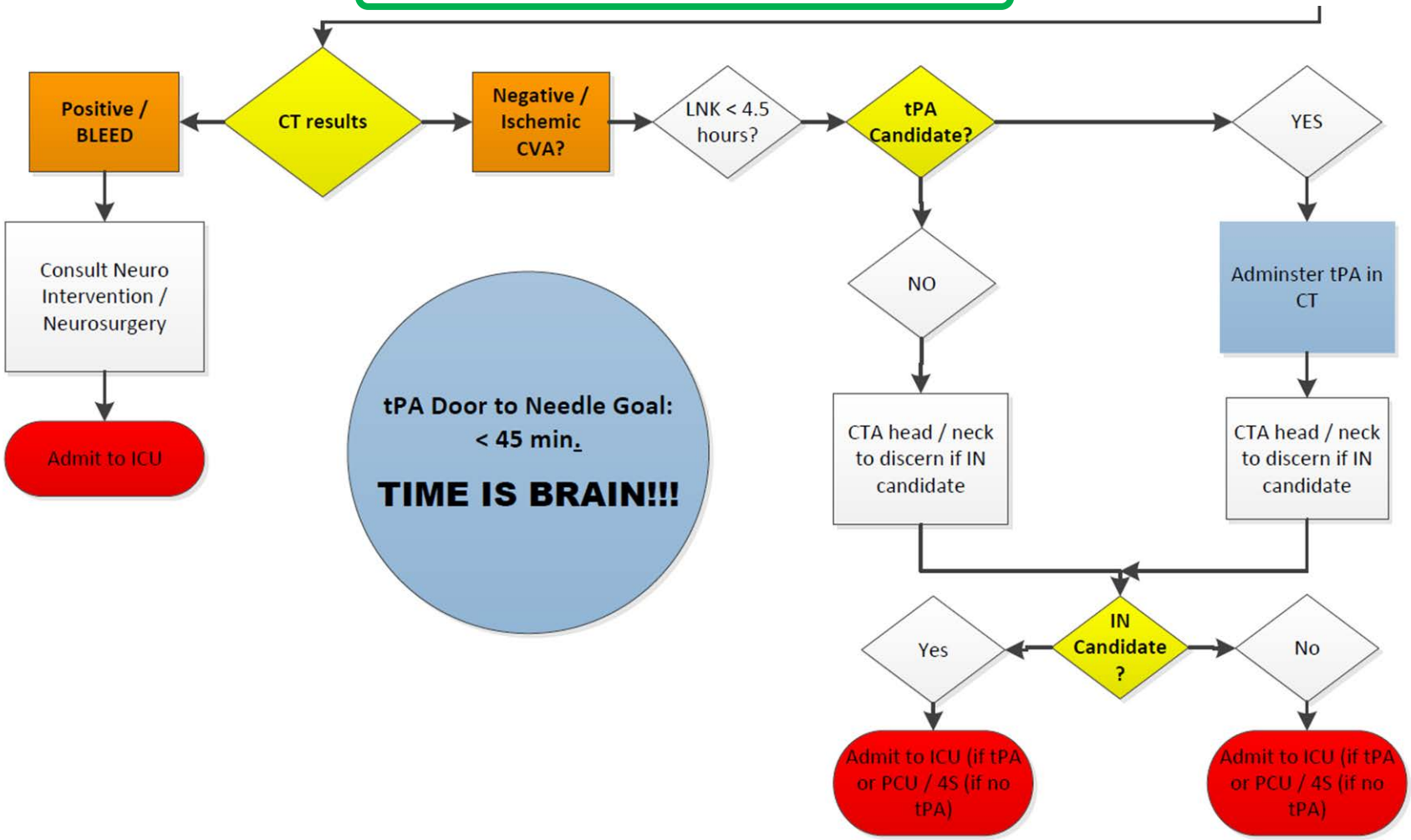
- tPA treatment rate 9.2%; 2rd highest in the NFD
- 69.7% DTN time <=60 min; #4 in the NFD

Strategies to Decrease Door-to-Needle Times



Strategies to Decrease Door-to-Needle Times

North Florida Regional Medical Center



Strategies to Decrease Door-to-Needle Times

North Florida Regional Medical Center

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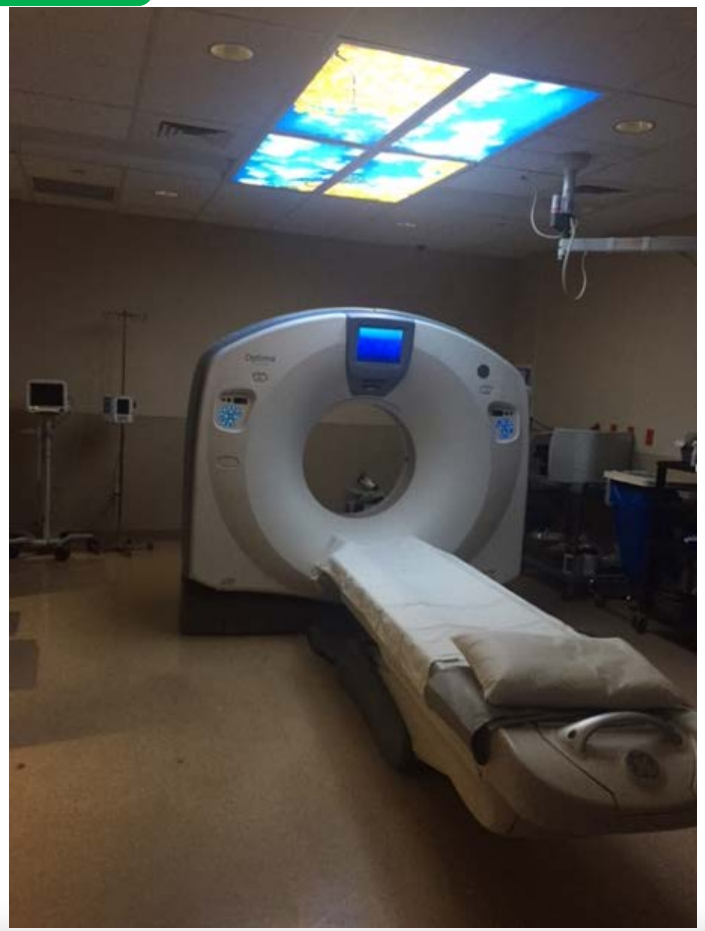
Staging Area in ED with weigh bed and Stroke Bag always on the ready!

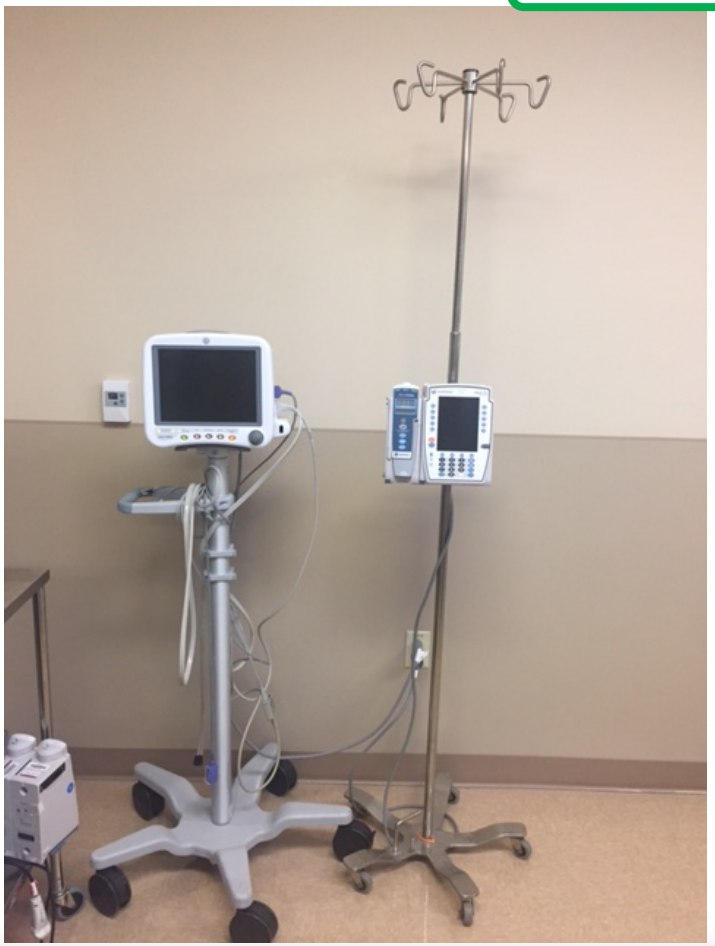
→→ →→

CT outfitted with IV pump, Pyxis with tPA, antihypertensives, Zofran, etc.



Strategies to Decrease Door-to-Needle Times

North Florida Regional Medical Center



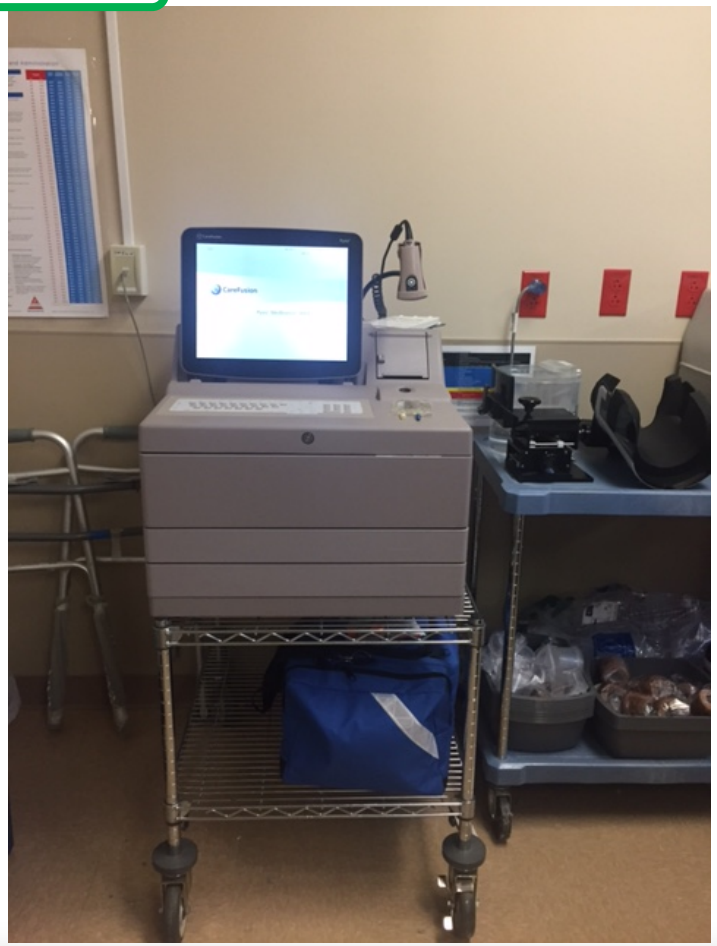
←←←←

Alaris Pump always ready and waiting in CT.

→→ →→

CT outfitted with Pyxis with tPA, hydralazine, labetolol, nicardipine, Zofran, D50W.

(Stroke bag for inpatient stroke alerts beneath pyxis.)



Strategies to Decrease Door-to-Needle Times

NFRMC Stroke Bag contents:

- Reference book
  - Stroke Alert checklist
  - Stroke Algorithm
  - tPA inclusion / exclusion
  - Pt./family education
  - tPA Dosing guide
  - Paper NIHSS
  - Consents
  - Pictorial illustration of Alaris pump set up for tPA administration
- Monitoring supplies
- IV start / lab / IStat supplies
- tPA administration supplies
  - 60 cc lock syringes for tPA waste
  - Pump tubing
  - Blunt tip needles
- Foley cath
- Dressing / gauze

Strategies to Decrease Door-to-Needle Times

- Code Stroke at North Florida Regional-HCA NFD

Strategies to Decrease Door-to-Needle Times

Strategies implemented at Fort Walton Beach Medical Center:

Stroke Team: Multidisciplinary team approach

- EMT(if patient arrives via ambulance)
- Stroke coordinator
- ER physician/ Neurologist/ Teleneurologist
- ED Nurse/ Code Responder/Nursing Supervisor
- ED unit secretary
- CT technician
- Radiologist
- Pharmacy
- Laboratory

Strategies to Decrease Door-to-Needle Times

Strategies implemented at Fort Walton Beach Medical Center:

- EMS notification prior to arrival
- Overhead announcement “Stroke Alert”
- Stroke Protocol and established stroke alert ED algorithm
- Rapid Interpretation of brain imaging
- Rapid Laboratory testing

Strategies to Decrease Door-to-Needle Times

Strategies implemented at Fort Walton Beach Medical Center:

- Pharmacy staff education
- Improved communication with ER
- tPA log book
- Computer order entry of tPA order prior to CT confirmation
- Participation with the Stroke Committee

Strategies to Decrease Door-to-Needle Times

Thrombolytic Checklist for Acute Ischemic Stroke

Shaded areas may exclude a patient from receiving t-PA

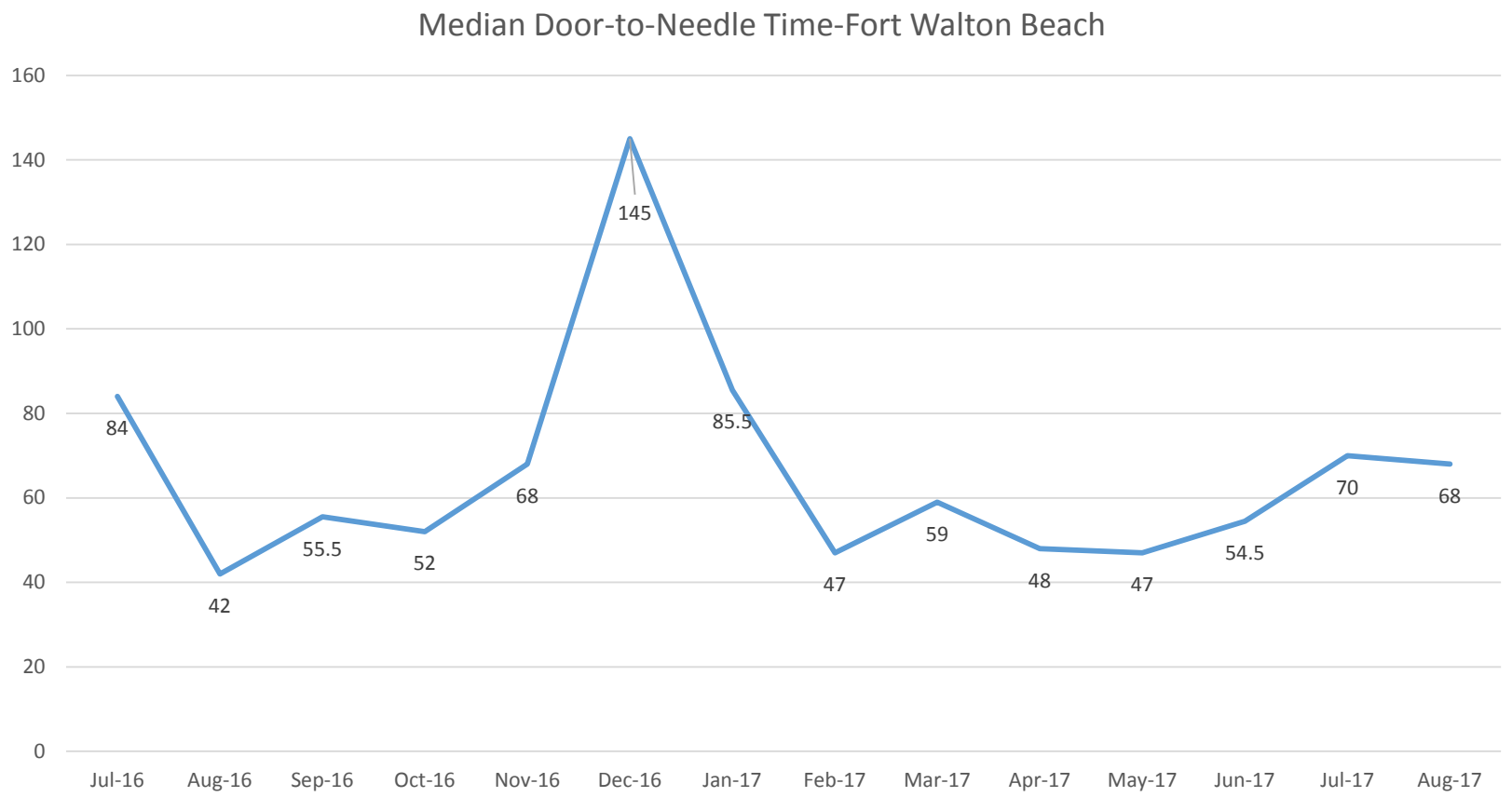
Thrombolytic Therapy Inclusion Criteria 1- 4	Yes	No
1. Age 18 years or older		
2. Clinical diagnosis of ischemic stroke with measurable neurologic deficit		
3. Time of last known to be well less than 4.5 hours before thrombolytic treatment would begin		
4. CT excludes hemorrhage		
Thrombolytic Therapy Contraindications 5-19	**Yes**	**No**
5. Current use of oral anticoagulants with a PT>15 seconds & INR >1.7, or Platelets <100,000		
6. Platelet count < 100,000		
7. Use of heparin or low molecular weight heparin in the previous 48 hours **AND** have elevated PTT		
8. Previous stroke or head trauma in the past 3 months		
9. Prior history of intracranial hemorrhage		
10. Major surgery or trauma, or dental extraction within the preceding 14 days		
11. Persistent pre-treatment SBP >185mmHG or diastolic >110mmHg		
12. Rapid improving neurological signs or isolated, mild neurological deficits such as ataxia alone, sensory loss alone, dysarthria alone or minimal weakness		
13. Gastrointestinal or urinary bleeding within preceding 21 days		
14. Known/suspected infective pericarditis		
15. Pregnant female, or early post-partum up to four (4) weeks, or menses		
16. Clinical presentation suggestive of subarachnoid hemorrhage, even with normal Cat Scan		
17. Arterial puncture at a non-compressible site or lumbar puncture within 7 days		
18. Mitral stenosis with atrial fibrillation		
19. Any chest compressions		
Thrombolytic Therapy Relative Contraindications 20 – 26	**Yes**	**No**
20. NIHSS >22		
21. Age > 85		
22. Known arteriovenous malformation neoplasm, or aneurysm		
23. Uncontrolled HTN		
24. Witnessed seizure at stroke onset		
25. Blood glucose <50mg or >400mg		
26. Hemorrhagic eye disorder		
Extended Window 3 – 4.5 Hours, Additional Exclusions 27-30	**Yes**	**No**
27. Age > 80		
28. NIHSS > 25		
29. Patient on Coumadin (Warfarin) regardless of INR results		
30. Combination of prior stroke **AND** diabetes		

Signature of Reviewer: _____ **Date** _____ **Time**_____

File Under: Progress Notes

Fort Walton Beach Medical Center Thrombolytic Therapy Checklist	**Patient Sticker**

Strategies to Decrease Door-to-Needle Times



- tPA treatment rate 11%; highest in the NFD
- 47.9% DTN time <=60 min; #7 in the NFD

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Questions?