Acute Stroke
Shifting From Informed Consent to Informed Refusal of Intravenous Tissue-Type Plasminogen Activator

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In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Decker et al.1 have described a qualitative study to better define the type of information and the best methods of display to enable patients to express their preferences toward emergency treatment of stroke with intravenous tissue-type plasminogen activator (tPA). Ten focus group interviews were conducted among stroke survivors, caregivers, emergency physicians, and nurses, and then based on their findings, the Rapid Evaluation for Stroke Outcomes using Lytics in a Vascular Event (RESOLVE) decision aid tool was developed. This work is an extension of the previous work by the authors in developing a similar tool for shared decision making in nonurgent percutaneous cardiac interventions. They found that patients and caregivers want simple graphs that show the increased chance of recovering to independence, not to perfection, in general and for their individual circumstances, while understanding the risks involved. Providers had concerns about the process itself and voiced skepticism about the underlying efficacy and safety data of tPA, particularly the risk of hemorrhage and the ability to have meaningful discussions of risk and benefit in such an emergent setting. This skepticism is echoed in the recent modification of the American College of Emergency Physicians statement downgrading the level of evidence supporting the use intravenous tPA in stroke and calling for shared decision making, when feasible, between the patient (and his or her surrogate) and a member of the healthcare team that includes a discussion of potential benefits and harms before the decision whether to administer intravenous tPA for acute ischemic stroke.2 In the next phase of work, the RESOLVE tool will be pilot tested in real-patient encounters.

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However, decision making in acute stroke occurs in the context of a time-critical condition not an elective procedure or treatment, with 1.9 million neurons and 14 billion synapses dying every minute,3 often in a patient who is not competent to participate in an informed decision. Frightened patients or family members, tremendous time pressure, and inconsistent interpretations of the evidence do not create an environment conducive for informed consent. A study of the quality of informed consent during acute telestroke encounters suggests that perceptions of the nature and completeness of informed consent vary substantially according to the perspective of the rater.4 If we accept that true informed consent is an unlikely outcome in an acute stroke emergency, then, we must consider alternative ethical frameworks for emergency decision making, namely shared decision making, presumed consent, and exception from informed consent.

Shared decision making has been identified as a vital element of high-quality, high-value medical care, most notably in preference-sensitive conditions. Preference-sensitive conditions include those where treatment equipoise exists, such as angina, back pain, or early-stage cancer—where legitimate treatment options coexist each with substantial trade-offs between benefits and risks to the patient, without an obvious recommendation.5 In these circumstances, the optimal treatment for any given patient should be tailored to that patient’s preferences. Treatment for acute ischemic stroke does not seem to meet the definition of a preference-sensitive condition because tPA is the only efficacious therapy for acute stroke widely available; the data supporting its ability to restore functional independence are based on multiple randomized trials, and it is unlikely that patients’ preferences or values will influence a decision to the contrary in this context. What is clear is that all treatment decisions about tPA should be those most consistent with what patients would express if they were able to fully understand the evidence of risk and benefit and articulate these wishes at the time of treatment. Rare is the case when patients are so well informed and prepared for a possible stroke that they arrive with a written note pinned to their shirt requesting tPA.6

If emergency and front-line providers have concerns about recommending intravenous tPA, it might be because of either a perceived small effect size of tPA’s benefit, increased risk of harm, or a desire for a better understanding of patients’ preferences. Because thrombolytic therapy for acute myocardial infarction has a smaller magnitude of benefit than it does in stroke and yet has been readily embraced by the emergency medicine community, it seems unlikely that the controversy is driven by the effect size of tPA treatment in stroke. However; there is a substantial increase in risk of acute bleeding with tPA in stroke compared with myocardial infarction, and this seems to be a major point of lingering concern despite the
fact that the measures of benefit of tPA incorporate this risk of harm. Recent data from malpractice claim that systematic review demonstrates that 95% of claims are for failure to administer tPA, rather than complications of treatment, and cases where defense expert witnesses have argued for the lack of tPA efficacy data as a valid reason for nontreatment usually were ruled in favor of plaintiffs.7

The data supporting the safety and efficacy of intravenous tPA are substantial and have been validated in multiple randomized trials across several continents and in postapproval registries. The use of intravenous tPA is endorsed at the highest levels of evidence from multiple US and international professional societies, and 5 recent large randomized clinical trials of intravenous tPA followed by endovascular thrombectomy provide further evidence of the safety and efficacy of reperfusion therapy in acute stroke.8 Intravenous tPA administered within the first 90 minutes after stroke onset is 18.5x more likely to benefit than harm adults with acute stroke, 8.8x more likely in the 91- to 180-minute interval, and 5.0x more likely in the 181- to 270-minute interval.9 This time-dependent benefit is supported by studies conducted in Get With the Guidelines-Stroke,10 the world’s largest hospital-based stroke registry with >3 million stroke admissions captured and >70000 patients receiving tPA analyzed. After adjustment for patient and hospital characteristics, more rapid administration of tPA was associated with reductions of in-hospital all-cause mortality (adjusted odds ratio, 0.89 [95% confidence interval, 0.83–0.94]; P<0.001), symptomatic intracranial hemorrhage (adjusted odds ratio, 0.83 [95% confidence interval, 0.76–0.91]; P<0.001), and increased discharge to home (adjusted odds ratio, 1.14 [95% confidence interval, 1.09–1.19]; P<0.001). This real-world registry experience confirms that the time-dependent nature of the benefits of intravenous tPA and the overall extremely low rates of symptomatic intracerebral hemorrhage are not just confined to teaching hospitals but occur in community hospitals across the United States that made up 35% of the 1030 hospitals in the study. Data from Get with the Guidelines-Stroke also confirm that >25% of patients who do not receive tPA because of mild or rapidly improving stroke are unable to return home or ambulate without assistance at discharge.11 Additional data from validated risk scores could potentially be incorporated over time into the RESOLVE tool to reflect real-world experience of harm.12,13

To address potential concerns that patients, given the proper amount of time and information, would express a preference to reject intravenous tPA treatment, Chiong et al14 surveyed older US adults about their preferences for treatments based on scenarios of stroke and cardiac arrest and found that the vast majority would request thrombolysis after stroke. If we agree that in most or all acute stroke cases, informed consent is not truly possible, either because the patient’s cognitive capacity or the circumstances prohibit it, then presumed consent based on information about what most patients would likely want if given the opportunity to reflect thoughtfully should be a guiding principle. Chiong et al14 found that when an incapacitated older patient’s treatment preferences are unknown and surrogate decision makers are unavailable, there are equally strong empirical grounds for presuming individual consent to thrombolysis for stroke as for presuming individual consent to cardiopulmonary resuscitation. In life-threatening emergencies involving incapacitated patients without surrogates, clinicians routinely intervene without obtaining informed consent, applying the presumption that reasonable people would consent to treatment in such circumstances.15 A follow-up study by Chiong et al14 confirms that the inability to consent does not diminish the desirability of stroke thrombolysis by older adults. Among 2154 US adults aged ≥50 years who read vignettes in which they had either had an acute ischemic stroke and could be treated with thrombolysis or had a sudden cardiac arrest and could be treated with cardiopulmonary resuscitation, participants were asked whether they would want the intervention and whether they would want the intervention even if their informed consent could not be obtained. Older adults were as likely to want stroke thrombolysis when unable to consent (78.1%) as when asked directly (76.2%), whereas older adults were more likely to want cardiopulmonary resuscitation when unable to consent (83.6% compared with 75.9%). These findings provide empirical support for recommendations to treat ischemic stroke with thrombolysis in appropriate emergency circumstances under a presumption of consent.17,18

Finally, one might consider that the concept of exception from informed consent could guide decision making in acute stroke. In their guidance on emergency research, the Food and Drug Administration defines emergency research requiring an exception from informed consent as investigations that involve human subjects who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory) and who, because of their condition (eg, traumatic brain injury), cannot provide informed consent. The research must have the prospect of direct benefit to the patient and must involve an investigational product that, to be effective, must be administered before informed consent from the subject or the subject’s legally authorized representative can be obtained.19 The studies of Chiong et al14,16 provide empirical evidence that patients would generally choose to opt in to a treatment, such as intravenous tPA, even without capacity to consent at the time, as there is a direct benefit expected and clear evidence of harm that would occur by delays in delivering the therapy.

The fact that tPA is associated with an increased risk of harm at the hands of the physician who administers the medication has resulted in an erroneous assumption that in order for treatment with tPA to be ethically appropriate, patients and surrogates must be comprehensively educated about the precise risks and benefits of tPA and then provide fully informed consent to the treatment. The traditional concept of informed consent is inappropriate because the context is not conducive to the kind of decision making we expect in nonurgent conditions. What is important in this setting is that physicians rapidly and efficiently provide the most essential information about the expected benefit of tPA in addition to the risks that would form the basis for refusing the treatment and then attempt to identify any legitimate reasons for refusal. Among patients with little expected benefit from intravenous tPA, the genuine act of refusal might be more common, and a tool such as RESOLVE that identifies these relatively uncommon patients could be valuable in the
acute setting for both patients and providers by highlighting the fact that most patients are expected to benefit from the drug. This applies especially to older patients and those with milder deficits.

Therefore, the goal of the tPA conversation should be to inform patients of the treatment plan and allow for appropriate informed refusals of tPA after a brief summary of the risks and benefits, ideally presented in a patient-centered manner suggested by the work of Decker et al. Reasonable individuals when presented with these options and the strength of the data would be expected to choose to undergo tPA treatment, and in practice, it is extremely unusual for eligible patients to refuse tPA therapy when it is offered. Honoring the appropriately informed patient's right to refuse therapy, when it does occur, is an important component of respecting patient autonomy.

The recent American College of Emergency Physicians controversy underscores the continued therapeutic nihilism that surrounds acute stroke. The time is long overdue to reformulate the notion of obtaining informed consent for intravenous tPA, particularly in the first 3 hours of stroke, into that of obtaining informed refusal. Eligible patients with stroke should receive intravenous tPA as rapidly as possible, just as they would resuscitate from cardiac arrest, unless they or their representatives can articulate a solid reason why therapy is not appropriate. To frame the decision as a matter of patient preference implies that the benefits of intravenous tPA are of such marginal advantage over other available treatments as to make this a preference-sensitive condition. With readily available and proven methods, such as telemedicine, to provide access to stroke expertise that can determine patient eligibility for thrombolysis and national campaigns to help reduce the door to needle time, the time has come for all hospitals to eradicate the disparity in how patients with stroke are considered for time-critical stroke therapy. Primum non nocere reminds us that as physicians, we must above all do no harm; but we must also acknowledge that harm may be caused not only by action but also by inaction or delay. In the words of William Shakespeare, "In delay, there lies no plenty" (Twelfth Night, Act II, Scene III). To treat or not to treat is no longer the question; how to treat more quickly and safely is what we should strive for with earnest.

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References


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