Precision Medicine to Support Decision Making for Reperfusion in Acute Ischemic Stroke

John Spertus MD MPH
Missouri/Lauer Endowed Chair and Professor,
University of Missouri - Kansas City
Clinical Director of Outcomes Research
Saint Luke’s Mid America Heart Institute

Portions of RESOLVE Tool Funded by AHA Outcomes Center Grant and AHA Accelerator Award
A Changing Landscape in Healthcare

- Volume-Driven Healthcare
- Value-Driven Healthcare
Improving Value in Healthcare

Value = Patient Experience + Outcomes

Cost

The Challenge:
Provide Care in a Highly Reliable Fashion
Patient-Centered Care is Challenging

Because Patients aren’t Average

Courtesy of Bob Cody MD, American Scientist 2007; 95:60-8
Improving Evidence-Based Medicine

Outcomes from a Study

Mean Treatment Difference

= Good Outcome  = Intermediate Outcome  = Bad Outcome

Risk Stratification
Delivering Precision Medicine Today

Knowledge Generation

Knowledge Translation Into Routine Clinical Care

Requires…
• Integration in workflow
• Clinically actionable information
Using Registries to Improve Healthcare

Prospective Data Collection - GTWG

Periodic Benchmark Reports for Quality Assurance

Creation of Predictive Models

Prospectively Improve Health

Requires a Novel IT Solution - ePRISM™

Improves Value with Precision Medicine

Supports Quality Assessment/Improvement through Benchmarking
The Challenge of tPA in Ischemic Stroke

Should I lyse this patient?
Will it cause a bleed?
Will they die?
Are there really any benefits from treating this patient?

- Emergent situation
- Accurate evaluation
- CT Scan
- tPA is time-sensitive

How can we communicate the risk, benefits and options of treatment?
tPA, even in Ideal Patients, has the Worst Performance
The Gap in Stroke Care

1M Strokes in GTWG

600,599 Ischemic Strokes

Presentation (IQR) time: 165’ (62-465)

24,894 Rxed with t-PA (4.1% of all Ischemics)

If ~40% present w/in 2°, why are more of the 240,000 patients not treated?

- Mild Stroke = 13%
- Clinical Improvement = 18%
- CT not done/Rx delay = 5%
- Protocol Exclusion = 14%
- ER Delay = 9%
- Significant Comorbidity = 8%

36% with disability or death at D/C

Fonarow G C et al. CCQO 2010;3:291-302
Barber et al. Neurology 2001;56:1015-1020
Huge Controversy in the Field

PEARLS FROM THE MEDICAL LITERATURE

The ACEP tPA Clinical Policy Saga Continues

by RYAN PATRICK RADECKI, MD, MS

The changes enshrined in this draft are substantial. The 2013 version made two recommendations regarding the use of IV tPA in the emergency
ACEP CRITICAL QUESTION – Is IV tPA safe and effective for acute ischemic stroke patients if given within 3 hours of symptom onset?

ACEP Patient Management Recommendations

- **Level A recommendations.** The increased risk of symptomatic intracerebral hemorrhage (approximately 7% compared to a baseline of 1%) must be considered when deciding whether to administer IV tPA to acute ischemic stroke patients.

- **Level B recommendations.** With a goal to improve functional outcomes, IV tPA may be given to carefully selected acute ischemic stroke patients within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication.

- **Level C recommendations.** Shared decision-making between the patient (and/or their surrogate) and a member of the healthcare team must include a discussion of potential benefits and harms prior to the decision whether to administer IV tPA for acute ischemic stroke. (Consensus recommendation)
Translating Knowledge to the Bedside

Outcomes/CER/Clinical Trials ➔ Prediction Models ➔ Improved Health

Core 1: Developing the Models ➔ Delivering the Evidence

Core 2: Developing Useful Outputs ➔ Patients using the data

Core 3: Implementing the Models ➔ Physicians using the data

PRISM

Improved Health

Delivering the Evidence

Patients using the data

Physicians using the data

Core 2: Developing Useful Outputs

Core 3: Implementing the Models

Core 1: Developing the Models

Outcomes/CER/Clinical Trials

Prediction Models

Improved Health
Creating RESOLVE

◆ Step 1 – Define Information for Patients and Providers

» What is a ‘good’ or ‘bad’ outcome?
» What information is needed to make a decision?
» How should it be presented?
Patient-Centered Decision Support in Acute Ischemic Stroke
Qualitative Study of Patients’ and Providers’ Perspectives

Carole Decker, RN, PhD; Emily Chhatriwalla, RD; Elizabeth Gialde, RN, MSN; Brian Garavalia, PhD; Debbie Summers, RN, MSN; Miriam E. Quinlan, MPH; Eric Cheng, MD; Marilyn Rymer, MD; Jeffrey L. Saver, MD; Er Chen, MPP; David M. Kent, MD, MS; John A. Spertus, MD, MPH

Background—National guidelines endorse recombinant tissue-type plasminogen activator (r-tPA) in eligible patients with acute ischemic stroke to improve patients’ functional recovery. However, 23% to 40% of ideal candidates with acute ischemic stroke for reperfusion are not treated, perhaps because of the difficulty in explaining the benefits and risks of r-tPA within the frenetic pace of emergency department care. To support better knowledge transfer and creation of a shared decision-making tool, we conducted qualitative interviews to define the information needs and preferred presentation format for stroke survivors, caregivers, and clinicians considering r-tPA treatment.

Methods and Results—A multidisciplinary team used qualitative research methods to identify informational needs and strategies for describing the benefits and risks of r-tPA in a clinical setting. Through focus groups (n=10) of stroke survivors (n=39) and caregivers (n=24) and individual interviews with emergency physicians (n=23) and advanced practice nurses (n=20), several themes emerged. Survivors and caregivers preferred a broader definition of a good outcome (independence, rather than no significant disability), simpler graphs as compared with detailed pictographs, and presentation of both population and individualized benefits (framed positively) and risk of receiving r-tPA. Some physicians expressed skepticism with the data and the ability to present risk/benefit information emergently, whereas other physicians and most advanced practice nurses thought such information would improve care. Physicians stressed the importance of presenting the risk of thrombolytic-related intracranial hemorrhage.

Conclusions—This study suggests that a positively framed risk–benefit tool with graphical presentations of general and patient-specific risk estimates could support patients and providers in considering r-tPA for acute ischemic stroke.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01864928.
(Circ Cardiovasc Qual Outcomes. 2015;8:S109-S116. DOI: 10.1161/CIRCOUTCOMES.115.002003.)
Qualitative Research Goal & Methods

- **Goal:** Explore patient/family/caregiver experience with stroke & their informational needs

- **Qualitative Approach (phenomenological exploration)**
  - Patient Focus Groups
    - UCLA Hospital Stroke Support groups
    - Saint Luke’s Hospital Stroke Support groups
    - American Stroke Foundation Support groups (KC)
    - New Bethel Church stroke-affected members
  - Provider Focus Groups – National
    - Emergency Medicine Physicians (EMP) – n=23
    - APNs (Neuro and Emergency) - n=20
  - Recorded, transcribed, analyzed (constant comparison)
Findings

◆ A ‘good’ outcome is mRS=0-2, not 0-1
◆ Survivors typically state that they do not recall being educated about acute stroke or its treatment
◆ Information is wanted – by patients & family
◆ Visual information needed for explaining a stroke
◆ Prefer text alongside pictures
Defining Best Data Presentation Formats

◆ Provide patients alternative risk representations
  – Pictographs, Vertical/Horizontal/Stacked Bar Charts

◆ Assess focus with eye-tracking technology
  – Measures the areas on the graph that are studied
  – Measures the length of time each area is studied

◆ Test successful knowledge transfer
Bar graph look zones

Outcome at 90 Days

Risk of Bleeding: tPA: 6.4%  No tPA: 0.6%
Outcome at 90 Days

Risk of Bleeding: tPA: 6.4%  No tPA: 0.6%
Creating RESOLVE

◆ **Step 1 – Define Information for Patients and Providers**
  » What is a ‘good’ or ‘bad’ outcome?
  » What information is needed to make a decision?
  » How should it be presented?

◆ **Step 2 – Rebuild Stroke-TPI Model**
  » Simplified 3-item Stroke Severity Item used
  » 5 other elements needed: Age, SBP, Diabetes, Glucose and Time from Symptom to Treatment
The Modified Stroke-TPI

Development and validation of a simplified Stroke–Thrombolytic Predictive Instrument

ABSTRACT

Objectives: The Stroke–Thrombolytic Predictive Instrument (Stroke-TPI) predicts the probability of good and bad outcomes with and without recombinant tissue plasminogen activator (rtPA). We sought to rebuild and externally validate a simpler Stroke-TPI to support implementation in routine clinical care.

Methods: Using the original derivation cohort of 1,983 patients from a combined database of randomized clinical trials (NINDS [National Institute of Neurological Disorders and Stroke] 1 and 2; ATLANTIS [Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke] A and B; and ECASS [European Cooperative Acute Stroke Study] II), we simplified the Stroke-TPI by reducing variables and interaction terms and by exploring simpler (3- and 8-item) stroke severity scores. External validation was performed in the ECASS III trial (n = 821).

Results: The following 6 variables were most predictive of good outcomes: age, systolic blood pressure, diabetes, stroke severity, symptom onset to treatment time, and rtPA therapy. Treatment effect modifiers included onset to treatment time and systolic blood pressure. For the models predicting a bad outcome (modified Rankin Scale [mRS] score ≥5), significant variables included age, stroke severity, and serum glucose. rtPA therapy did not change the risk of a poor outcome. Compared with models using the full NIH Stroke Scale, models using the 3-item severity score showed similar discrimination and excellent calibration. External validation on ECASS III showed similar performance (C statistics 0.75 [mRS score ≤1] and 0.80 [mRS score ≤2]).

Conclusion: A simpler model using a 3-item stroke severity score, instead of the 15-item NIH Stroke Scale, has similar prognostic value and may be easier to use in routine care. Future studies are needed to test whether it can improve process and clinical outcomes. Neurology® 2015;85:1-8
### Final Models

**Final Model for Very Good Outcome** *(mRS = 0-1)*

- rPA treatment
- Age (+10y)
- Systolic BP (+20mmHg)
- Diabetes
- 3-item stroke scale (+1pt)
- Time from sx onset to treatment (+1h)
- Treatment x Systolic BP
- Treatment x time
- Age x stroke scale

**Final Model for Good Outcome** *(mRS = 0-2)*

- rPA treatment
- Age (+10y)
- Systolic BP (+20mmHg)
- Diabetes
- Glucose
- 3-item Stroke Severity

---

**Requires Only 6 Variables:**

- Age
- Symptom Onset
- SBP
- Diabetes
- Glucose
- 3-item Stroke Severity
Validation of RESOLVE

Figure 1a: Derivation

Functionally Normal/Near-normal (mRS <=1)
- Observed
- Predicted

Functionally Independent (mRS <=2)
- Observed
- Predicted

Severe Disability/Death (mRS > 5)
- Observed
- Predicted

Figure 1b: Validation

Functionally Normal/Near-normal (mRS <=1)
- Observed
- Predicted

Functionally Independent (mRS <=2)
- Observed
- Predicted
Creating RESOLVE

◆ Step 1 – Define Information for Patients and Providers
  » What is a ‘good’ or ‘bad’ outcome?
  » What information is needed to make a decision?
  » How should it be presented?

◆ Step 2 – Rebuild Stroke-TPI Model
  » Simplified 3-item Stroke Severity Item used
  » 5 other elements needed: Age, SBP, Diabetes, Glucose and Time from Symptom to Treatment

◆ Step 3 – Program ePRISM
  » Patient/Family Educational Documents
  » Physician Decision Aid
**Risk Models**

\[
\eta = \beta_0 + \beta_1 x_{T,1} + \ldots + \beta_n x_{T,n} \\
\eta = \beta_1 x_{T,1} + \ldots + \beta_n x_{T,n} \\
\eta_i = \beta_{i,0} + \beta_{i,1} x_{T,1} + \ldots + \beta_{i,n} x_{T,n} \\
\mu_i = \begin{cases} 
\pi_i & i = 1 \\
\pi_i - \sum_{j=1}^{i-1} \pi_j & i = 2, \ldots, s \\
1 - \sum_{j=1}^{i-1} \pi_j & i = s+1
\end{cases}
\]

where \( \pi_i = \Phi^{-1}(\eta_i) \)

\[
\left(\eta_{LO}, \eta_{HI}\right) = \eta \pm F^{-1}_V \left(1 - \frac{\alpha}{2}\right) \sqrt{\varphi^2 + \sigma^2}
\]

\[
\sigma^2 = \begin{bmatrix} 
1 & x_{T,1} & \ldots & x_{T,n} \\
\vdots & \vdots & \ddots & \vdots \\
x_{T,1} & x_{T,1} & \ldots & x_{T,n}
\end{bmatrix}
\]

**Decision Support Tools**
The RESOLVE Tool for Stroke

**Treatment Benefits**

Outcome at 90 Days

- 43 people were normal or near normal
- 20 people were moderately disabled
- 20 people were severely disabled
- 17 people died

**Risk of Bleeding**

- tPA: 6.4%
- No tPA: 0.6%

**Treatment Risks**

The chart shows the chance of patients with symptoms or slight disability 90 days after stroke.

- 77% with tPA
- 70% without tPA

The chart shows the chance of patients with a severe disability 90 days after stroke.

- 8% with tPA
- 8% without tPA
Ischemic Stroke

**Benefits**

Chance of No Symptoms or Slight Disability (mRS 0-2) at 90 Days

*Benefit is likely 3 times greater than shown considering improvement across all functional levels*

Risk of Severe Disability or Death (mRS 5-6) at 90 Days

*The rt-PA bar above incorporates symptomatic ICH risk of 3% *

---

**Risks**

The ePRISM Decision Tool - Physician

Developed with funding by researchers at Saint Luke's Hospital of Kansas City

The RESOLVE Tool
Revised 05/27/2014
What RESOLVE is and isn’t..

RESOLVE is…
- A calculator of a validated, published risk model
- A means of presenting results to patients and physicians
- A means of engaging and educating patients

RESOLVE isn’t…
- A means of recommending treatment
  » Just presents data
- A means of making a diagnosis
- A means of monitoring outcomes
Accessing RESOLVE

- EMR Integration
- Web-based Application
- Mobile Device
Implementation Strategies

- Use in Stroke Center ED
- Use in Tele-Stroke Support

Run Local
Conclusion

◆ Patients want to be involved in treatment decisions
  – Want general and personal outcomes
  – Emphasize the benefits, but share the risks

◆ RESOLVE is a Powerful Tool to…
  – Provides Evidence-based Estimates of Outcomes to…
    » Support Medical Decision-making
    » Engage Patients/Family in Understanding Risks and Benefits
    » Potentially Improve Treatment and Outcomes

◆ Addresses ACEP demands for risks, benefits and SDM