Using a Patient-Centered Utility to Drive a Bayesian Adaptive Enrichment Trial of Treatments for Acute Stroke

Roger J. Lewis, MD, PhD
Department of Emergency Medicine
Harbor-UCLA Medical Center
David Geffen School of Medicine at UCLA
Los Angeles Biomedical Research Institute
Berry Consultants, LLC

Financial Disclosures and Thanks

- Berry Consultants, LLC
  - Multiple clients (including Stryker)
- Support from
  - National Institutes of Health
    - NINDS
    - NHLBI
    - NIGMS
- Octapharma AG

- Thanks to DAWN Study team, especially
  - Tudor G. Jovin, MD
  - Raul G. Nogueira, MD
  - Jeffrey L. Saver, MD
  - Todd Graves, PhD

Research

International Journal of Stroke WSO

Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods

International Journal of Stroke
2017, Vol. 12(6) 641–652
© 2017 World Stroke Organization
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/1747493017730341
journals.sagepub.com/home/wso
SAGE

Tudor G Jovin[1], Jeffrey L Saver[2], Marc Ribo[3], Vitor Pereira[4], Anthony Furlan[5], Alain Bonafe[6], Blaise Baxter[7], Rishi Gupta[8], Demetrius Lopes[9], Olav Jansen[10], Wade Smith[11], Daryl Gress[12], Steven Hetts[13], Roger J Lewis[14], Ryan Shields[15], Scott M Berry[16], Todd L Graves[16], Tim Malisch[17], Ansaar Rai[18], Kevin N Sheth[19], David S Liebeskind[2] and Raul G Nogueira[20]

International Journal of Stroke 2017;12(6):641-652.

Clinical Setting

- Adult patients with acute ischemic stroke
  - 6 to 24 hours since time last seen well (TLSW)
  - Beyond the time window for tPA and for approved clot retrieval strategies
  - Few treatment options, facing life-long disability
- This population is heterogeneous with respect to stroke severity and size of "core" on imaging
  - Some have a large "core"—brain that is dead
  - Some have a small "core" and a large "penumbra" of brain that is potentially salvageable

DAWN Trial Objective

- Patients with clinical-imaging mismatch (CIM) may benefit from clot retrieval even if relatively long after symptom onset
- DAWN is a pivotal Bayesian, adaptive, enrichment clinical trial aiming to identify the broadest population of patients with CIM (based on core infarct size), if any, who experience long-term benefit from clot retrieval compared to standard medical care
- Our focus today is on the goal of using a patient-centered outcome measure

Modified Rankin Scale (mRS)

Level	Description
0	No symptoms
1	No significant disability --able to perform all usual activities
2	Slight disability --able to look after own affairs
3	Moderate disability --requires some help, but able to walk unassisted
4	Moderately severe disability --assistance needed for walking and bodily needs
5	Severe disability --bedridden, requires constant nursing care
6	Dead

Modified Rankin Scale (mRS)

	Level	Description
Good	0	No symptoms
	1	No significant disability --able to perform all usual activities
	2	Slight disability --able to look after own affairs
Bad	3	Moderate disability --requires some help, but able to walk unassisted
	4	Moderately severe disability --assistance needed for walking and bodily needs
	5	Severe disability --bedridden, requires constant nursing care
	6	Dead

7

Dichotomization of the mRS

- Clinicians, statisticians, and regulators are comfortable with the dichotomized mRS
  - Traditionally the mRS is dichotomized, limiting us to benefit within the ranges of 0-2 or 3-6
  - Terms are used to blur the boundaries between scores of 0 to 2, e.g., "functional independence"
  - Analyses of dichotomized data are considered "valid" despite the loss of information on differences of value to patients

8

The Value or Utility of Outcomes

- Neurological outcomes are varied and complex with multiple domains and evaluators
- Different patients and their families value outcomes differently
  - "I just want him alive" (5 > 6)
  - "She'd never want to live like that" (6 > 5)
- The reported value of a given outcome may vary based on time and context
- There is no single utility function that represents everyone's values at all time points

9

How to Move Forward

- Treatment (and regulatory) decisions should be as patient-centered as possible
- When outcomes are complex, our goal should be to make a good-faith effort
  - To capture what is important to patients
  - To assign reasonable values to outcomes
  - To identify treatments that maximize the expected utility of patient outcomes
- Don't let the perfect be the enemy of the good

10

Benefit may Exist Across mRS Disability

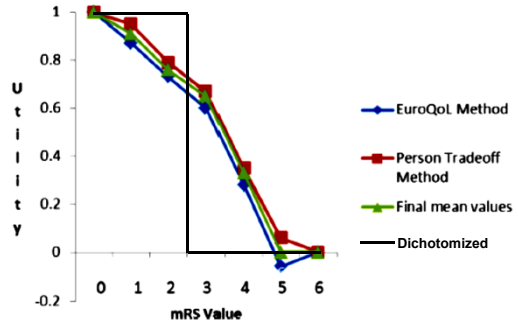
- Need a patient-centered approach sensitive to all important benefits: Utility Weighted mRS

mRS	0	1	2	3	4	5	6
Rivero-Arias et al	10	8.7	7.3	6.0	2.8	-0.1	0
Hong & Saver	10	9.5	7.9	6.7	3.5	0.1	0
DAWN	10	9.1	7.6	6.5	3.3	0	0

mRS	0	1	2	3	4	5	6
Dichotom-ized	10	10	10	0	0	0	0

11

Agreement Between Utility Functions



Stroke 2015;46:2238-2243

12

Adopting a Patient-Centered Approach to Primary Outcome Analysis of Acute Stroke Trials Using a Utility-Weighted Modified Rankin Scale

Napasri Chaisinanunkul, MD; Opeolu Adeoye, MD, MS; Roger J. Lewis, MD, PhD; James C. Grotta, MD; Joseph Broderick, MD; Tudor G. Jovin, MD; Raul G. Nogueira, MD; Jordan J. Elm, PhD; Todd Graves, PhD; Scott Berry, PhD; Kennedy R. Lees, MD; Andrew D. Barreto, MD, MS; Jeffrey L. Saver, MD; for the DAWN Trial and MOST Trial Steering Committees*

Background and Purpose—Although the modified Rankin Scale (mRS) is the most commonly used primary end point in acute stroke trials, its power is limited when analyzed in dichotomized fashion and its indication of effect size challenging to interpret when analyzed ordinally. Weighting the 7 Rankin levels by utilities may improve scale interpretability while preserving statistical power.

Methods—A utility-weighted mRS (UW-mRS) was derived by averaging values from time-tradeoff (patient centered) and person-tradeoff (clinician centered) studies. The UW-mRS, standard ordinal mRS, and dichotomized mRS were applied to 11 trials or meta-analyses of acute stroke treatments, including lytic, endovascular reperfusion, blood pressure moderation, and hemicraniectomy interventions.

Results—Utility values were 1.0 for mRS level 0; 0.91 for mRS level 1; 0.76 for mRS level 2; 0.65 for mRS level 3; 0.33 for mRS level 4; 0 for mRS level 5; and 0 for mRS level 6. For trials with unidirectional treatment effects, the UW-mRS paralleled the ordinal mRS and outperformed dichotomous mRS analyses. Both the UW-mRS and the ordinal mRS were statistically significant in 6 of 8 unidirectional effect trials, whereas dichotomous analyses were statistically significant in 2 to 4 of 8. In bidirectional effect trials, both the UW-mRS and ordinal tests captured the divergent treatment effects by showing neutral results, whereas some dichotomized analyses showed positive results. Mean utility differences in trials with statistically significant positive results ranged from 0.026 to 0.249.

Conclusions—A UW-mRS performs similar to the standard ordinal mRS in detecting treatment effects in actual stroke trials and ensures the quantitative outcome is a valid reflection of patient-centered benefits. (***Stroke***. **2015;46:2238-2243. DOI: 10.1161/STROKEAHA.114.008547.**)

13

Adaptive Enrichment Strategy

- Core infarct size thought to be most likely eligibility characteristic that might define differentially responding populations
- DAWN Strategy
  - Enroll up to 50 cc core infarct volume
  - Enrich by lowering upper limit (50 → 45 → 40 etc.) if that increases the likelihood of a positive trial
- All decisions based on probability of demonstrating improvement in mean uw-mRS with clot retrieval

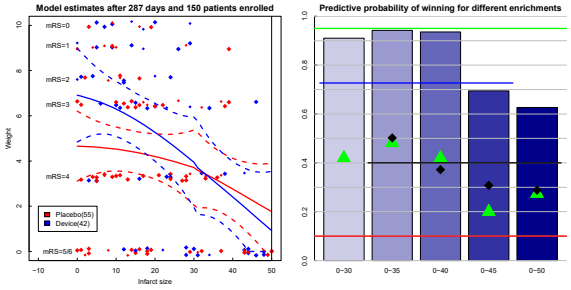
14

Pre-Specified Decision Rules

- DAWN Design used specific pre-specified rules
  - Timing of interim analyses [150, 200, … , 450]
  - Possible decisions, and criteria, at each analysis
  - Rules for early stopping [200, 250 …] based on probability of success > 95%, > 90%, > 85%, > 80%
  - Rules for early stopping for futility [150, 200 …] based on uniform probability of success < 10%
  - Enrichment
    - If it increases chance of positive trial by 10%
    - Eliminate populations based on core infarct size if < 40% chance of benefit in that population

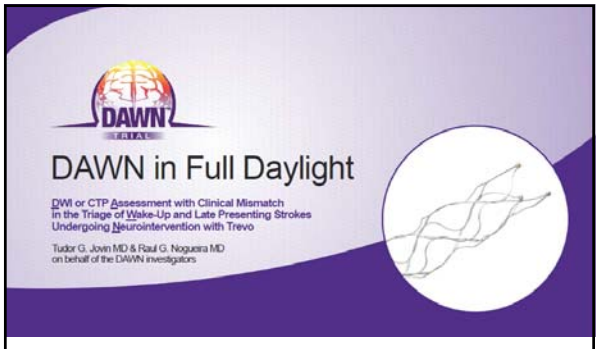
15

Simulation Data (n = 150)



Source: Todd Graves, PhD

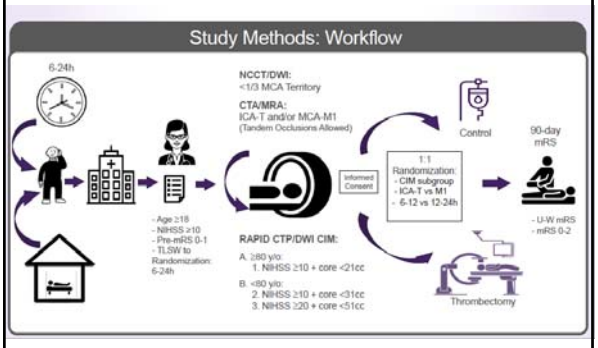
16



Presented at European Stroke Organization Meeting in Prague, May 2017.

Jovin TG, Nogueira RG, and for the DAWN investigators. DAWN in full daylight (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention). European Stroke Journal 2017;2(1S):494.

17



European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494.

18

Study endpoints

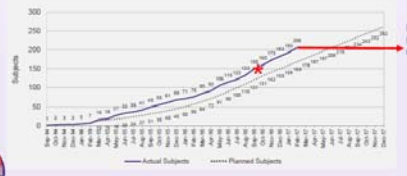
Primary endpoint	90-day disability assessed by the modified Rankin scale (mRS) • Assessed via Utility-Weighted mRS • Nested Dichotomous mRS 0-2
Secondary endpoints	• "Early response" at day 5-7/discharge, defined as a NIHSS drop of ≥10 points from baseline or NIHSS score 0 or 1 • All cause mortality rates • Median final infarct size at 24 (-6/+24) hours from randomization • Revascularization rates at 24 (-6/+24) hours from randomization • Treatment arm: reperfusion rates post device and post procedure by angiography core lab measurement of modified TICI > 2b
Primary safety endpoint	Stroke related mortality at 90 days
Secondary safety endpoint	• Incidence of SICH, by ECASS III definition, within 24 (-6/+24) hours post randomization • Incidence of neurological deterioration from baseline NIHSS score through day 5-7/discharge • Incidence of procedure-related and device-related serious adverse events through 24 (-6/+24) hours post randomization

European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 19

TRIAL ENROLLMENT RATE AND TERMINATION

Site Status			
Sites Qualified	36	Contracts Executed	31
Sites Initiated	30	Sites Activated to Enroll	30
IRB/EC Approvals	31	Subjects Enrolled	206

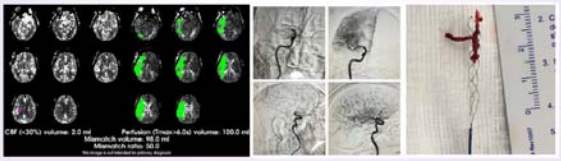
Actual / Projected Enrollment



*Boundary for first enrichment not crossed

European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 20

Results



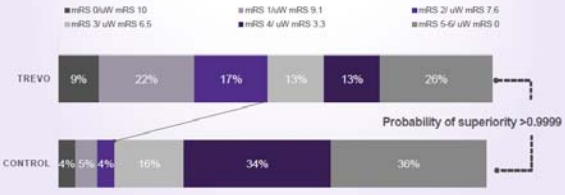
European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 21

Patient presentation

	Treatment arm N=107	Control arm N=99	P- value
Time since time last seen well to randomization (hrs)			
Mean ± SD Median (Q1, Q3) Range (min, max)	13.4 ± 4.1 12.2 (10.2, 16.0) (6.1, 23.5)	13.0 ± 4.5 13.2 (9.4, 15.6) (6.4, 23.9)	0.53
Stroke sub-population			
Wake up stroke	64.5%	47.5%	0.01
Witnessed stroke	10.3%	14.1%	0.52
Un-witnessed stroke	25.2%	38.4%	0.05

European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 22

Primary outcome



73% relative risk reduction of dependency in ADL's
NNT for any lower disability 2.0

European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 23

Co-primary endpoints

	Trevo	MM	Treatment benefit (95% CI)	Bayesian probability of superiority
Day 90 weighted mRS	5.5 ± 3.8	3.4 ± 3.1	2.1 (1.20, 3.12)	>0.9999*
Day 90 mRS (0-2)	48.6%	13.1%	35.5% (23.9%, 47.0%)	>0.9999*

NNT for 90-day functional independence = 2.8

*Similar to p<0.0001

European Stroke Organization Meeting in Prague, May 2017.
Jovin TG et al. European Stroke Journal 2017;2(1S):494. 24

Revisit: Moving Forward

- Treatment (and regulatory) decisions should be as patient-centered as possible
- When outcomes are complex, our goal should be to make a good-faith effort
  - To capture what is important to patients
  - To assign reasonable utilities to outcomes
  - To identify treatments that maximize the expected utility of patient outcomes
- Don't let the perfect be the enemy of the good
- Don't get too comfortable with tradition that is even worse

25

Conclusions

- In situations in which outcomes and the associated values are complex, the use of patient-centered utilities can provide clarity
- Utilities shouldn't be over-simplified or avoided out of habit or comfort
- Beware the argument that a simplified approach is "accepted" or will be "understood" by clinicians
- Our patients and families depend on us to conduct research that is relevant to them and what they hope to gain through medical care

26