ARTSS-2: FINAL RESULTS of a Pilot, Phase IIb, Randomized, Multi-center Trial of Argatroban in Combination with Recombinant Tissue Plasminogen Activator for Acute Stroke

Andrew D. Barreto, Gary A. Ford, Loren Shen, Claire MacDonald, Claudia Pedroza, Jon Tyson, Chunyan Cai, Mohammad H. Rahbar, James C. Grotta, for the *ARTSS-2 Trial Investigators*:

US PIs: Andrei Alexandrov, Steven Levine, Navi Sangha, Michael Mullen, James L Frey, John J. Volpi, Vivek Misra

UK PIs: Bart Piechowski, Christine Roffe, Anand Dixit, Martin James, Usman Khan, Jesse Dawson, Richard Perry, Joseph Devine

Other Contributors: Renga Pandurengan, Aisha S. Dickerson, Manouchehr Ardjomand-Hessabi, Amber Jacobs, Hari Indupuru, Rick Sline, Xiaobao Li, Rigo Delgado, Andrew Demchuk, Georgios Tsivgoulis, Marc Malkoff, Elaine McColl, Zahra Ajani, April Sisson

Feb 17, 2016

Disclosures

- Unapproved use of medication Argatroban

- Study Sponsors
  1. NIH/NINDS -- U.T. Houston SPOTRIAS Grant
  2. NIH/NINDS -- American Recovery and Reinvestment Act
  3. Diane and Harold Farb Stroke Fund
  4. GlaxoSmithKline & Mitsubishi Pharma Eu
     - Provided study medication
     - No role in design, analysis or presentation conclusions

Rationale

- **IV-tPA is insufficient in many cases**
  - Proximal occlusion recanalization rates: 13-20%
  - Re-occlusion rates substantial

- **Argatroban, direct thrombin inhibitor, may augment tPA**
  - ***Animal models:*** Increases the speed and completeness of recanalization

- **ARTSS-1 study** Stroke 2012, 43:770-775
  - Single-arm study of low-dose **Argatroban** + **tPA** (0.9mg/kg)
    - Argatroban bolus (1 μg/kg) started during tPA infusion
    - 48-hour infusion to target **1.75 × baseline PTT**
  - ≤4.5 Hours with proximal intracranial occlusions
  - N=65
  - Symptomatic ICH: **4.6%,** 95% CI: 0.9-12.9
  - Higher recanalization compared to historical controls [tPA-alone]

Study Purpose and Design

- **Determine safety and benefit of argatroban in tPA treated patients**
- **Phase IIb, randomized, multicenter, international** (US & UK)
- **PROBE, open-label with blinded:**
  - Imaging core (CT/MR and recanalization)
  - 90-day outcome assessments
- **3 arms (1:1:1); n=105**
  1. tPA (control)
  2. tPA + *low-dose* Argatroban (**1.75** × baseline PTT)
  3. tPA + *high-dose* Argatroban (**2.25** × baseline PTT)
- **Stratified Randomization**
  - Site
  - Risk of sICH: Hemorrhage After Thrombolysis (HAT) score
  - Terminal internal carotid artery occlusion
- **DSMB & Independent Safety Monitor**

Study Design

- **Primary Outcomes**
  - Safety: incidence of symptomatic ICH
    - Blood on CT + clinically sig. neuro worsening (treating physician or safety monitor)
      - No minimum NIHSS required
  - Efficacy: modified Rankin Scale 0-1 at 90-days

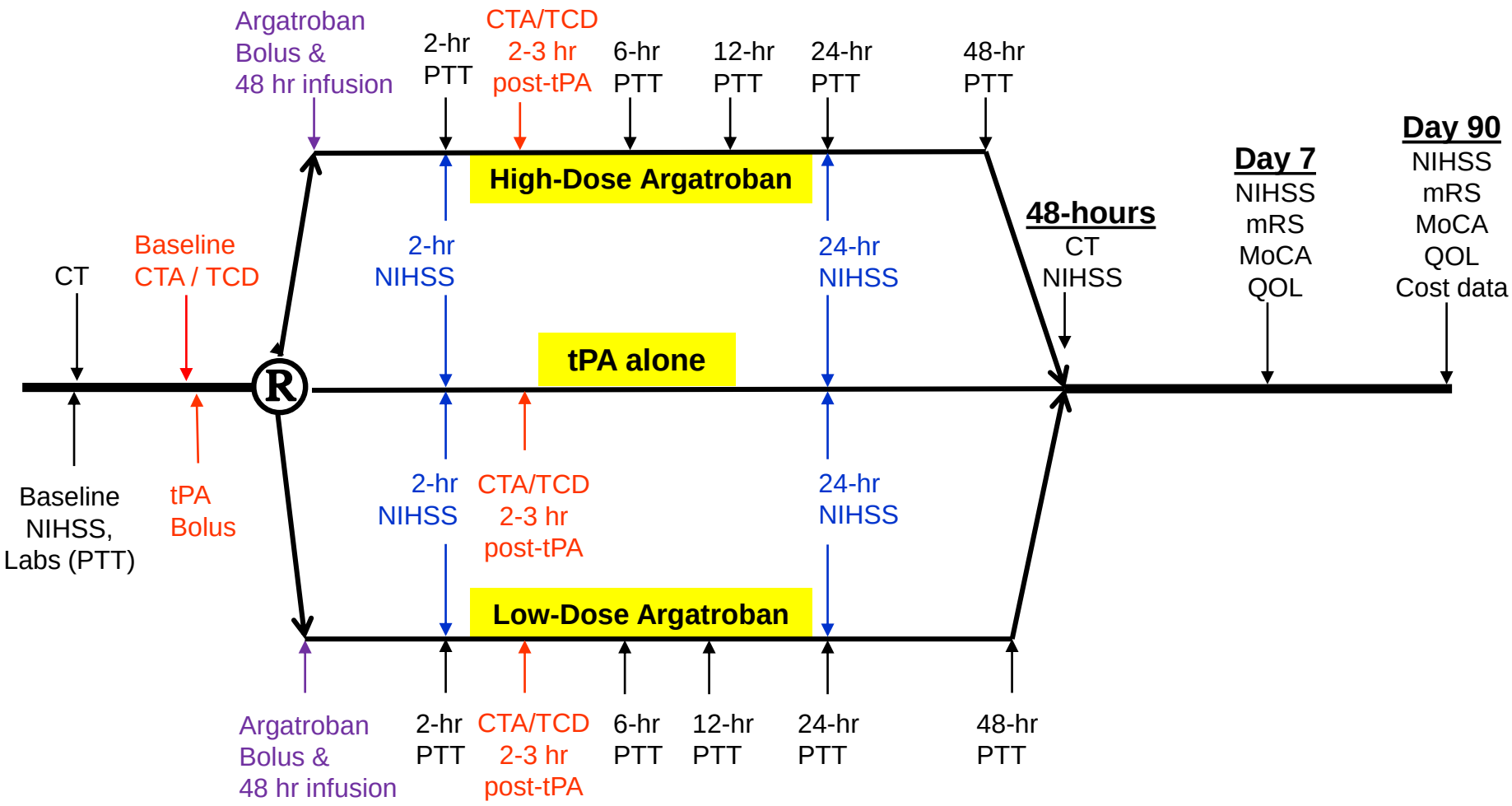
- **Analysis**
  - Bayesian and Frequentist Poisson regression – Relative Risk
    - The important clinical question is directly answered: "What is the probability of Argatroban+tPA superiority [c/w tPA alone]?"
  - Adjusted for stratification variables
  - Intent To Treat

- **Sample Size**
  - Pilot study with 105 planned enrollments
  - Objective of gaining useful preliminary safety & efficacy information

Patient Eligibility

1) Ischemic Stroke patients treated with IV-tPA
   - ≤4.5 hours according to each site's local standard
   - ECASS-3 exclusion criteria utilized
2) Age ≥ 18
3) NIHSS ≥ 10
   - Or any NIHSS with proximal, intracranial artery occlusion (TCD or CTA)
4) INR <1.6
5) Normal baseline PTT
6) mRS 0 or 1
7) Endovascular Therapy <u>not</u> allowed

ARTSS-2 Time Flow



Results

- Trial prematurely terminated after beneficial results of mechanical thrombectomy trials

- Dec 2011 – March 2015
  - 90 of planned 105 patients randomized
    - 1 patient lost-to-follow-up in High-Dose arm

Baseline Characteristics

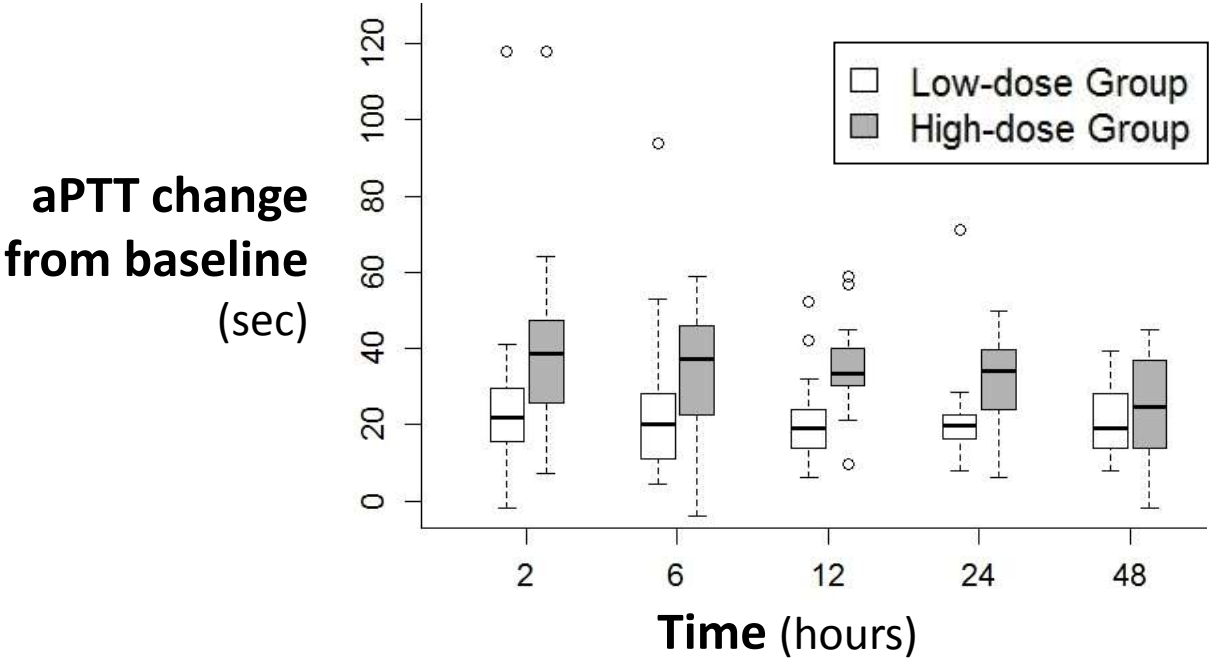
	Control (tPA-alone) N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31
Age mean ± SD	69 ± 15	71 ± 15	67 ± 13
Male n (%)	17 (59)	17 (57)	16 (52)
Stroke Onset to tPA bolus minutes mean ± SD	114 ± 43	134 ± 52	114 ± 46
Baseline NIHSS median (IQR)	15 (11, 20)	16 (11, 21)	13 (7, 17)
Glucose median, range	123, 69-418	130, 88-309	125, 86-494
Antithrombotic medications n (%)			
Aspirin	11 (38)	7 (24)	12 (39)
Clopidogrel	2 (7)	1 (3.5)	2 (7)
Warfarin	1 (4)	2 (7)	1 (3)
Past Medical History n (%)			
Prior stroke	3 (10)	3 (10)	5 (16)
Hypertension	25 (86)	24 (80)	25 (81)
Coronary Artery Disease	1 (4)	3 (10)	1 (3)
Diabetes mellitus	6 (21)	10 (33)	9 (29)
Congestive heart failure	6 (21)	1 (3)	6 (19)
Atrial fibrillation	5 (17)	7 (23)	11 (36)
ASPECTS score median (IQR)	10 (8, 10)	8 (6, 10)	9 (8, 10)

Baseline Characteristics

	Control (tPA-alone) N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31
Age mean ± SD	69 ± 15	71 ± 15	67 ± 13
Male n (%)	17 (59)	17 (57)	16 (52)
Stroke Onset to tPA bolus minutes mean ± SD	114 ± 43	134 ± 52	114 ± 46
Baseline NIHSS median (IQR)	**15 (11, 20)**	**16 (11, 21)**	**13 (7, 17)**
Glucose median, range	123, 69-418	130, 88-309	125, 86-494
Antithrombotic medications n (%)			
Aspirin	11 (38)	7 (24)	12 (39)
Clopidogrel	2 (7)	1 (3.5)	2 (7)
Warfarin	1 (4)	2 (7)	1 (3)
Past Medical History n (%)			
Prior stroke	3 (10)	3 (10)	5 (16)
Hypertension	25 (86)	24 (80)	25 (81)
Coronary Artery Disease	1 (4)	3 (10)	1 (3)
Diabetes mellitus	**6 (21)**	**10 (33)**	**9 (29)**
Congestive heart failure	6 (21)	1 (3)	6 (19)
Atrial fibrillation	**5 (17)**	**7 (23)**	**11 (36)**
ASPECTS score median (IQR)	**10 (8, 10)**	**8 (6, 10)**	**9 (8, 10)**

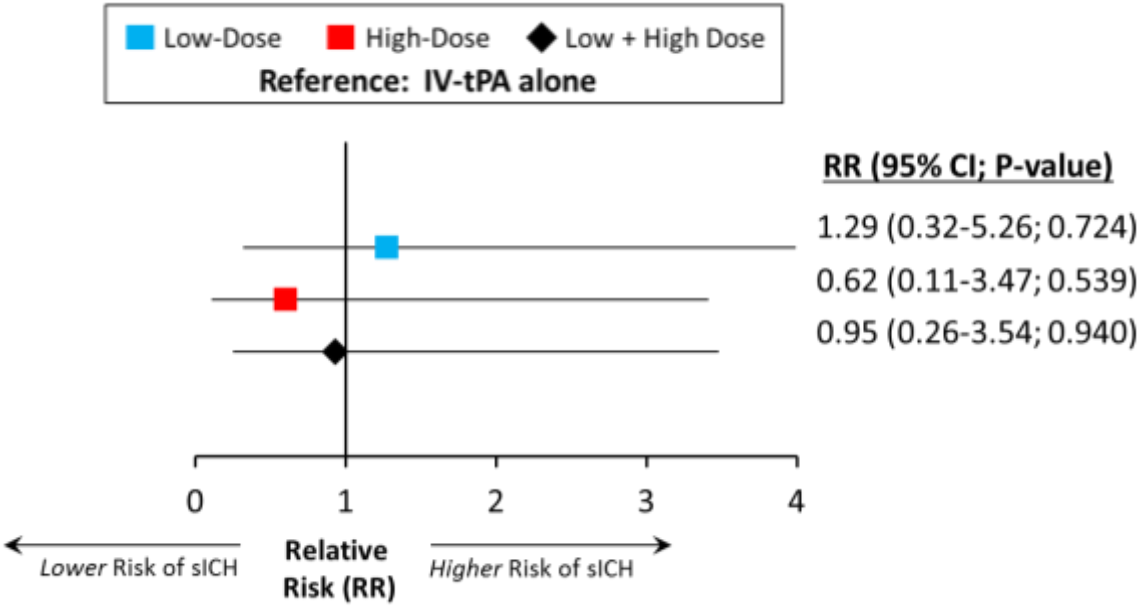
Anticoagulation Results

	Low-Dose Argatroban + tPA N=30	High-Dose Argatroban + tPA N=30
Minutes tPA bolus to Argatroban bolus median, range	59.5, 29-105	60.5, 30-102
Hours to (or above) 90% target aPTT median (IQR)	2.2 (2.0, 2.5)	2.0 (1.8, 2.6)
First aPTT after Argatroban bolus median (IQR)	49.4 (41, 55)	68.9 (54, 81)



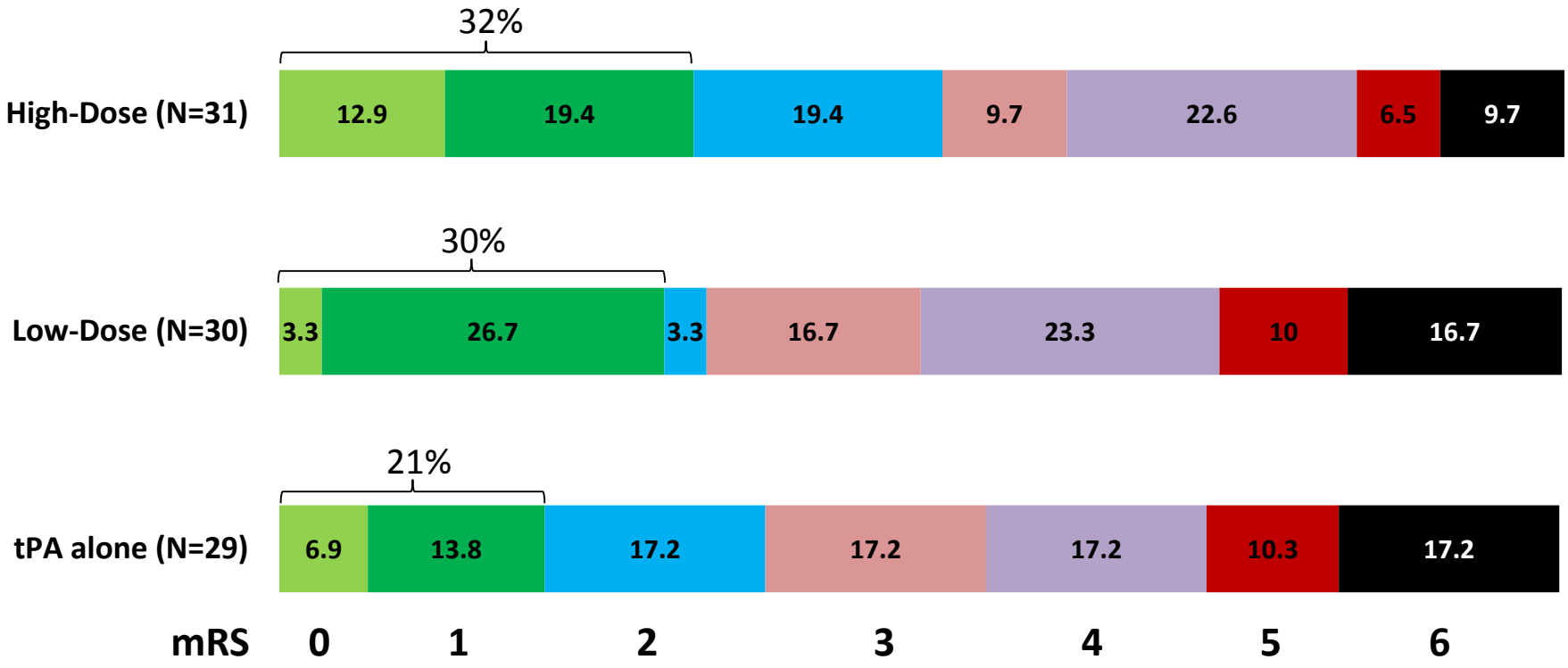
Safety Results

	Control (tPA-alone) N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31	Low + High-Dose Arg + tPA N=61
Symptomatic ICH n (%) *Intention to Treat*	3 (10.3%)	4 (13.3%)	2 (6.5%)	6 (9.8%)
PH-2 n (%)	3 (10.3)	1 (3.3)	2 (6.5)	3 (4.9)
PH-1 n (%)	1 (3.5)	3 (10.0)	0 (0)	3 (4.9)
Other serious bleeding adverse events n	2	1	0	1



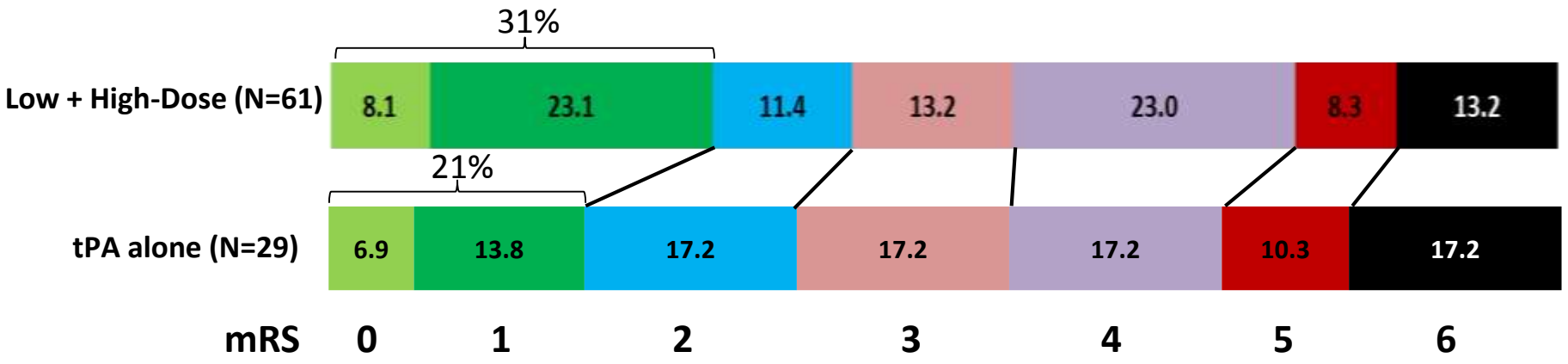
**1 patient randomized to High-Dose Argatroban never received drug.*

Primary Efficacy Outcome: Day 90 mRS



1 lost-to-follow-up case imputed using last observation carried forward (Day 7 mRS=4)

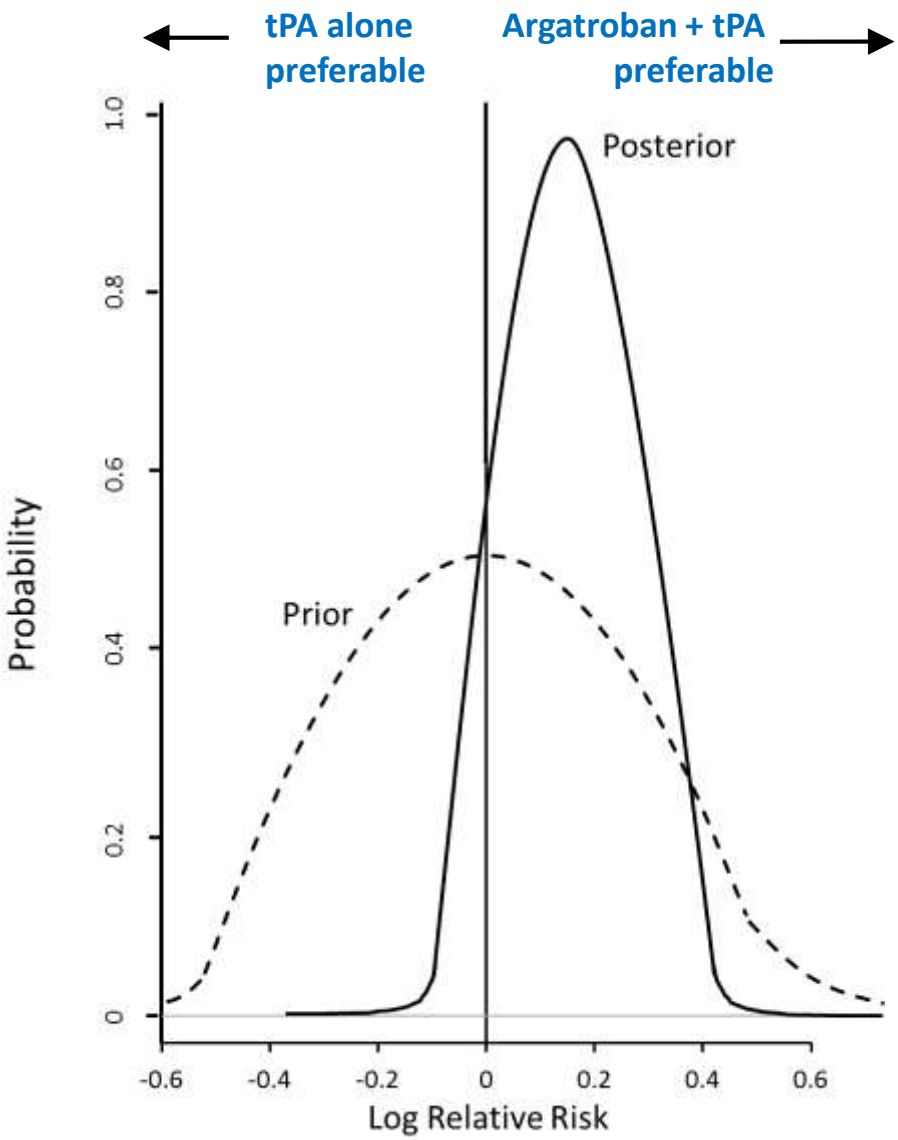
Primary Efficacy Outcome: Day 90 mRS



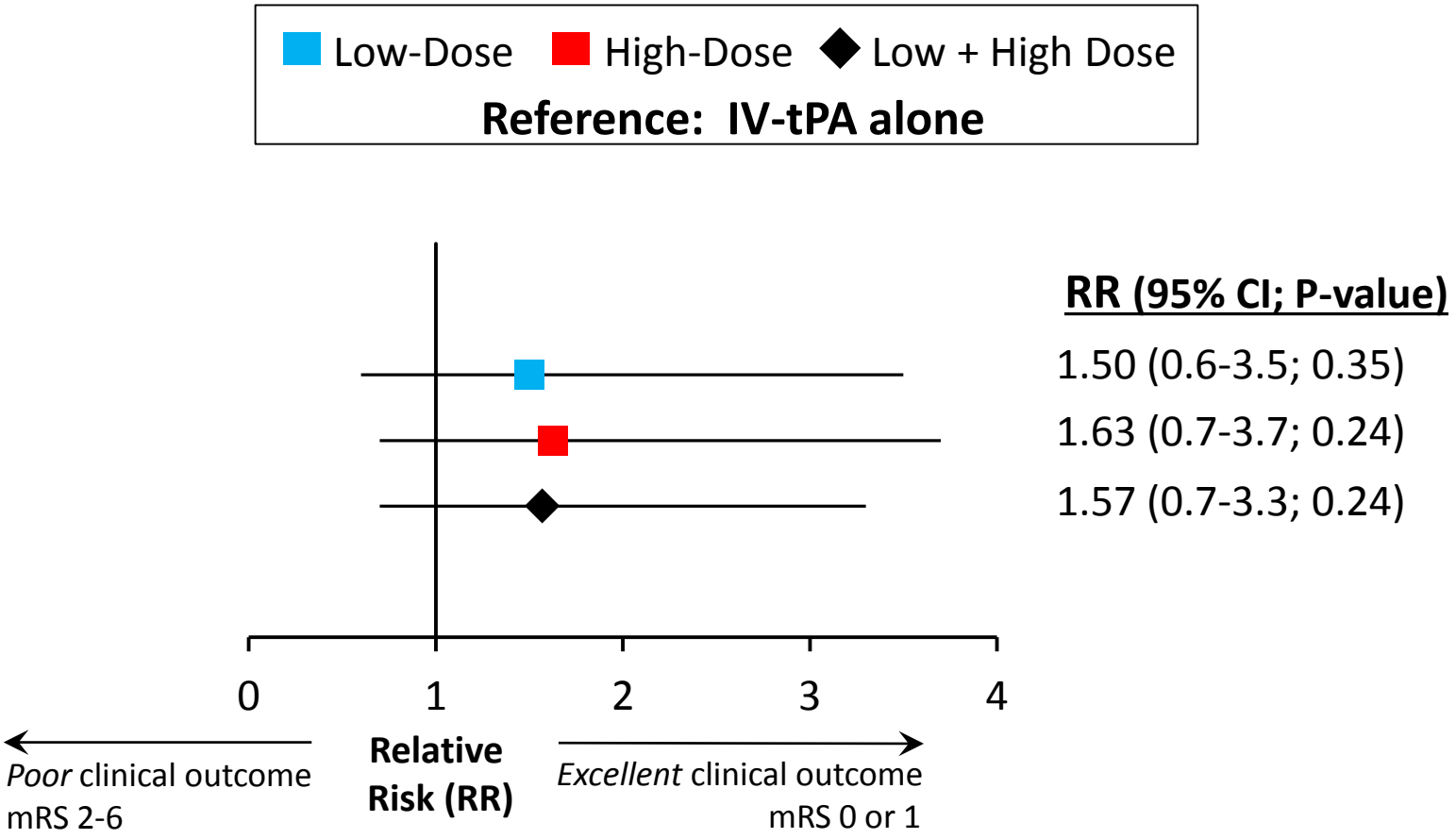
Primary Clinical Outcome - Bayesian – 90-day mRS 0-1

- **Prior**:
  - RR 1.0, 95% CrI of 0.3-3.0
    - Neutral prior assumes no benefit
      - Equal probability of benefit & harm

- **Posterior**: (Low+High-dose combined)
  - **RR 1.34, 95% CrI 0.68-2.76**
  - **79% probability of benefit (RR >1.0)**



Primary Clinical Outcome: mRS 0-1 at 90 days
Frequentist Approach - adjusted



Post-Hoc Exploratory Analyses

1) Ordinal Logistic Regression – 90-day mRS

- Adjusted for stratification variables
- mRS 5 & 6 combined

	Odds Ratio; 95%CI, p-value
High-Dose Argatroban	**2.03**; 0.8-5.1, 0.13
Low-Dose Argatroban	**1.23**; 0.5-3.1, 0.66
High + Low-Dose Argatroban	**1.58**; 0.7-3.5, 0.26

2) Symptomatic ICH SITS-MOST definition

	Control (tPA-alone) N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31	Low + High-Dose Arg + tPA N=61
sICH n (%)	0 (0%)	1 (3.3%)	2 (6.5%)	3 (4.9%)

Limitations

- **Small Sample Size**
  - Minor baseline imbalances
- **Open-label design**
  - Double-blinded deemed unfeasible
    (cost, complexity of sham aPTT results, etc)
- **Unknown safety of combination + Endovascular**
  - ARTSS-IA study - NCT02448069

Conclusion

- In patients treated with IV tPA, adjunctive argatroban appears safe

- Observed clinical benefit warrants further study in a definitive efficacy trial

UTHealth | Medical School
The University of Texas Health Science Center at Houston

UAB MEDICINE
NEUROSCIENCES
Comprehensive Stroke Center

BARROW Neurological Institute

SUNY DOWNSTATE Medical Center

KAISER PERMANENTE

HOUSTON Methodist NEUROLOGICAL INSTITUTE

Penn Medicine

WE MAKE LIVES BETTER
UT HEALTH SCIENCE CENTER SAN ANTONIO

Thank you for your attention

CTS Center for Clinical and Translational Sciences

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

University Hospitals of North Midlands NHS
NHS Trust

Royal Devon and Exeter NHS
NHS Foundation Trust

University College London Hospitals NHS
NHS Foundation Trust

NHS Greater Glasgow and Clyde

St George's Healthcare NHS
NHS Trust

Northwick Park & The North West London Hospitals NHS
NHS Trust

King's College Hospital NHS
NHS Foundation Trust

ADDITIONAL SLIDES

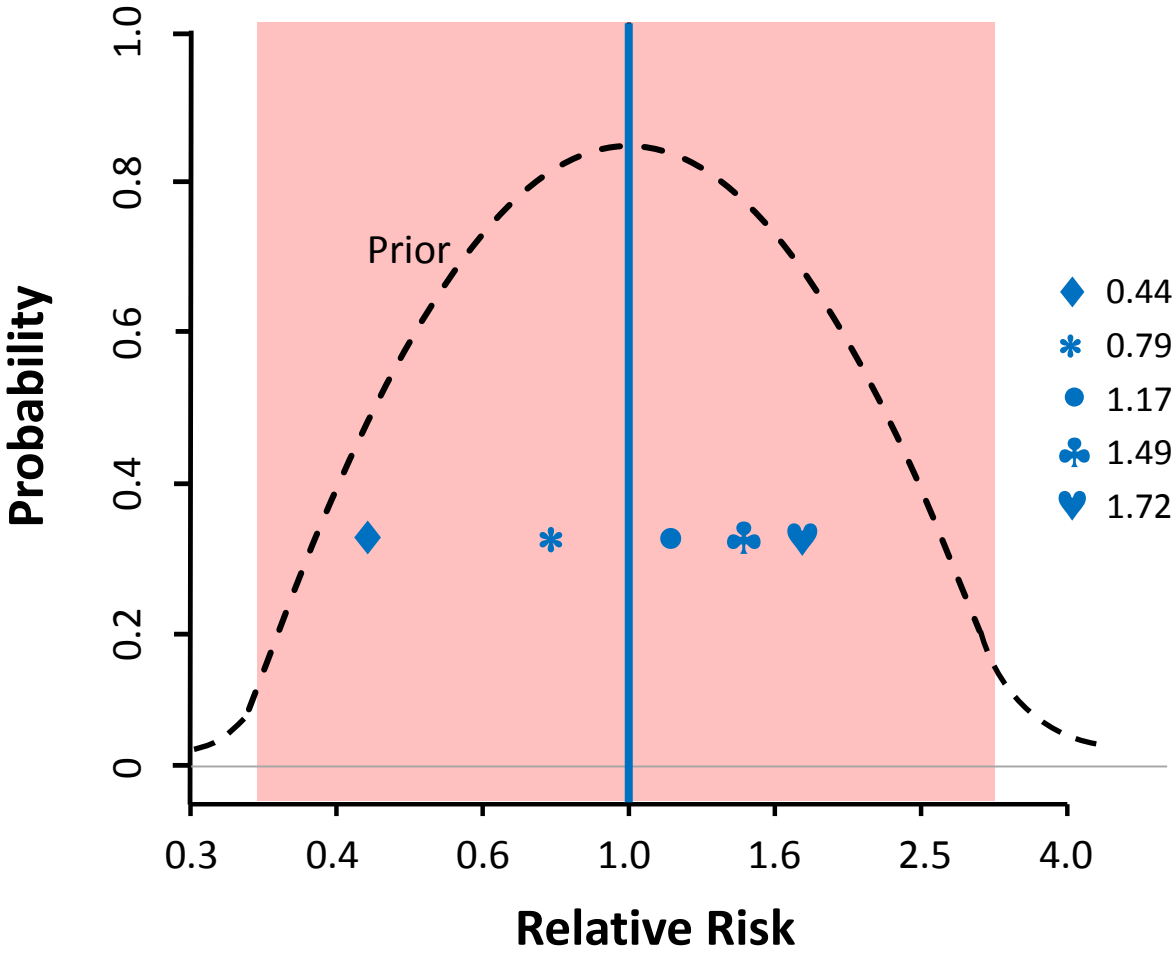
Bayesian Analysis Approach: 90-day mRS

Implausible that Argatroban+tPA benefit is:

- ***>30% greater benefit of hemicraniectomy***

  or

- ***>75% greater benefit of Stentreiver Endovascular***



♦ 0.44 - mRS >4 Hemicraniectomy
✻ 0.79 - mRS >3 Hemicraniectomy
● 1.17 - mRS 0-1 IV-tPA 3-4.5 hours
♣ 1.49 - mRS 0-1 IV-tPA ≤3 hours
♥ 1.72 - mRS 0-2 Stentreiver Endovascular

Recanalization Results

- 46 patients (51%) had both baseline and follow-up vessel imaging

	TREATMENT ARM					
Variable	**TPA-ALONE** (N=11)	**Low-Dose Arg** (N=20)	**High-Dose Arg** (N=15)	**RR (95% CI) p Low vs. tPA**	**RR (95% CI) p High vs. tPA**	**RR (95% CI) p Low+High vs. tPA**
VESSEL OCCLUSION, n(%)						
MCA	**9 (82)**	**16 (80)**	**13 (87)**			
M1	9 (100)	11 (69)	7 (54)			
M2	0	5 (31)	6 (46)			
Terminal ICA	**2 (18)**	**2 (10)**	**2 (13)**			
Vertebro-basilar	**0**	**2 (10)**	**0**			
COMPLETE RECANALIZATION at 2 hours, n(%)	**2 (18.2)**	**3 (15)**	**4 (26.7)**	**0.83 (0.2-4.2) p=0.82**	**1.47 (0.3-6.6) p=0.62**	**1.10 (0.3-4.5) p=0.9**

Baseline Characteristics – Vascular Imaging

	Control (tPA-alone)	Low-Dose Argatroban + tPA	High-Dose Argatroban + tPA
Vascular imaging n (%)	N=11	N=20	N=15
CTA	9 (82)	16 (80)	12 (80)
TCD	2 (18)	4 (20)	3 (20)
Clot location n (%)			
MCA	9 (82)	16 (80)	13 (87)
M1	9 (100)	11 (69)	7 (54)
M2	0	5 (31)	6 (46)
Terminal ICA	2 (18)	2 (10)	2 (13)
Posterior Circulation	0 (0)	2 (10)	0 (0)

sICH - SITS-MOST definition

Method of Analysis	Control (tPA-alone) N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31	Low + High-Dose Arg + tPA N=61
Intention to Treat, n (%)	**0** (0%)	**1** (3.3%)	**2** (6.5%)	**3** (4.9%)
As Treated*, n (%)	**1** (3.3%)	**1** (3.3%)	**1** (3.3%)	**2** (3.3%)

**One patient randomized to High-Dose Argatroban never received the drug (thus was a tPA-alone if using the as-treated approach).*

Other Adverse Events

	tPA-alone N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31
Adverse events (AE), no. #, mean (no. per person)	65, 2.2	112, 3.7	88, 2.9
Probably related to Argatroban, no.	-	3	2
Possibly related to Argatroban, no.	-	27	32
No. of patients with at least one AE, n (%)	20 (69.0)	27 (90.0)	25 (80.7)
No. of patients with at least one SAE, n (%)	14 (48.3)	15 (50.0)	15 (48.4)
Serious adverse events (SAE), no. #	22	29	24
Probably related to Argatroban, no.	-	0	0
Possibly related to Argatroban, no.	-	5	5
Not related to Argatroban, no.	-	24	19

Randomization Covariate Balance Results

Factor	Level	Treatment Group			P-value
		tPA-alone N=29	Low-Dose Arg + tPA N=30	High-Dose Arg + tPA N=31	
HAT score	0-2 (low-risk)	25 (86)	25 (83)	26 (84)	1.0
	3-5 (high-risk)	4 (14)	5 (17)	5 (16)	
Terminal ICA occlusion	N/A (no vessel imaging)	8 (28)	8 (27)	7 (23)	0.97
	No	18 (62)	18 (60)	21 (68)	
	Yes	3 (10)	4 (13)	3 (10)	
Site (US/UK)	All US sites	21 (72)	22 (73)	22 (71)	0.98
	All UK sites	8 (28)	8 (27)	9 (29)	