Antihypertensive Treatment of Acute Cerebral Hemorrhage 2 trial: Primary Results

Adnan I. Qureshi MD, Yuko Y. Palesch PhD

For the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial investigators

Supported by:

- **Grants from the National Institute of Neurological Disorders and Stroke (U01-NS062091, PI: Qureshi; and U01-NS061861, PI: Palesch).**

- **Chiesi USA, Inc., and Astellas Pharma, Inc., supplied intravenous nicardipine for study use.**

Primary hypothesis

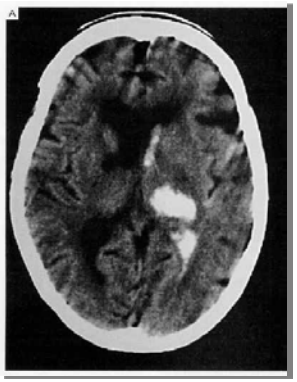
- Intensive treatment of elevated systolic blood pressure (≥180 mm Hg) reduces the likelihood of death or disability (modified Rankin scale 4-6) at 3 months after intracerebral hemorrhage, by at least 10 % absolute difference compared with standard treatment.
- Standard treatment goals: 140-179 mm Hg
- Intensive treatment goals: 110-139 mm Hg
- Target recruitment: 1280 subjects
- Presumed mechanism of therapeutic benefit: reduction in rate of hematoma expansion

Qureshi AI, Palesch YY. Neurocrit Care. 2011;15(3):559-76

Trial design: ATACH-2

re. Qureshi AI, Palesch YY. Neurocrit Care. 2011;15(3):559-76.

- Systolic BP ≥180 mm Hg
- GCS ≥ 5
- Hematoma vol <60cm3



IV Rx

≥180 mm Hg

≥140 mm Hg

Randomize 1:1 and initiate IV nicardipine

140-179 mm Hg

110-139 mm Hg

CT scan NIHSS score

SAEs/ deaths

Modified Rankin scale by blinded investigator

Onset

4.5 h

24 h

90 d

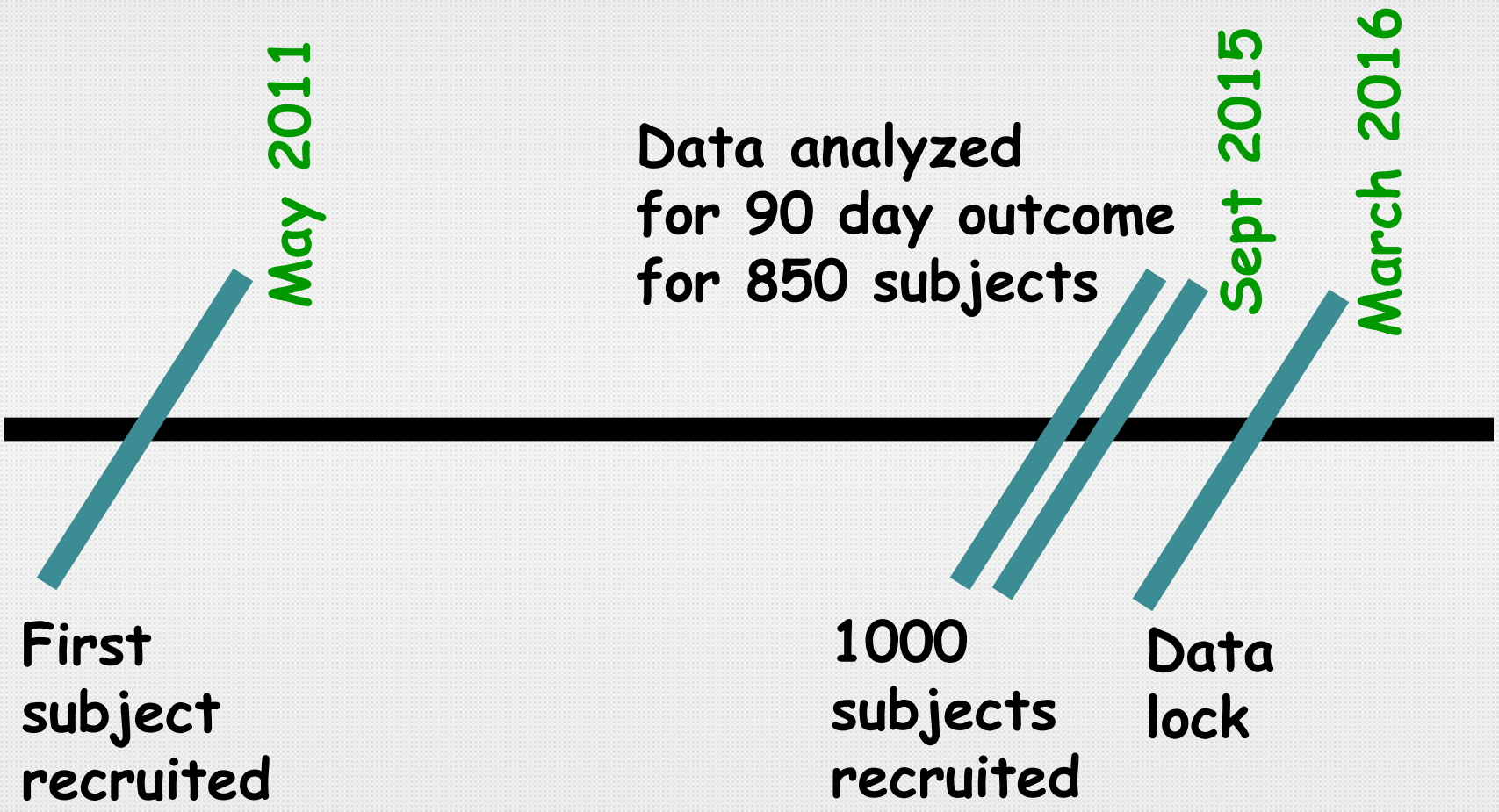
Interim analysis:

For assessment of futility, the stochastic curtailment method based on conditional power

INTERIM ANALYSIS SAMPLE	EFFICACY ASSESS-MENT: P-VALUE	FUTILITY ASSESSMENT: CONDITIONAL POWER UNDER CURRENT TREND	
		USING TRT=0 AS REFERENCE	USING TRT=1 AS REFERENCE
N=425	0.5280	42.68%	75.42%
N=640	0.9516	29.47%	33.75%
N=850	0.9053	9.11%	4.73%

Both were below the pre-specified threshold and DSMB recommended stopping the study for futility.

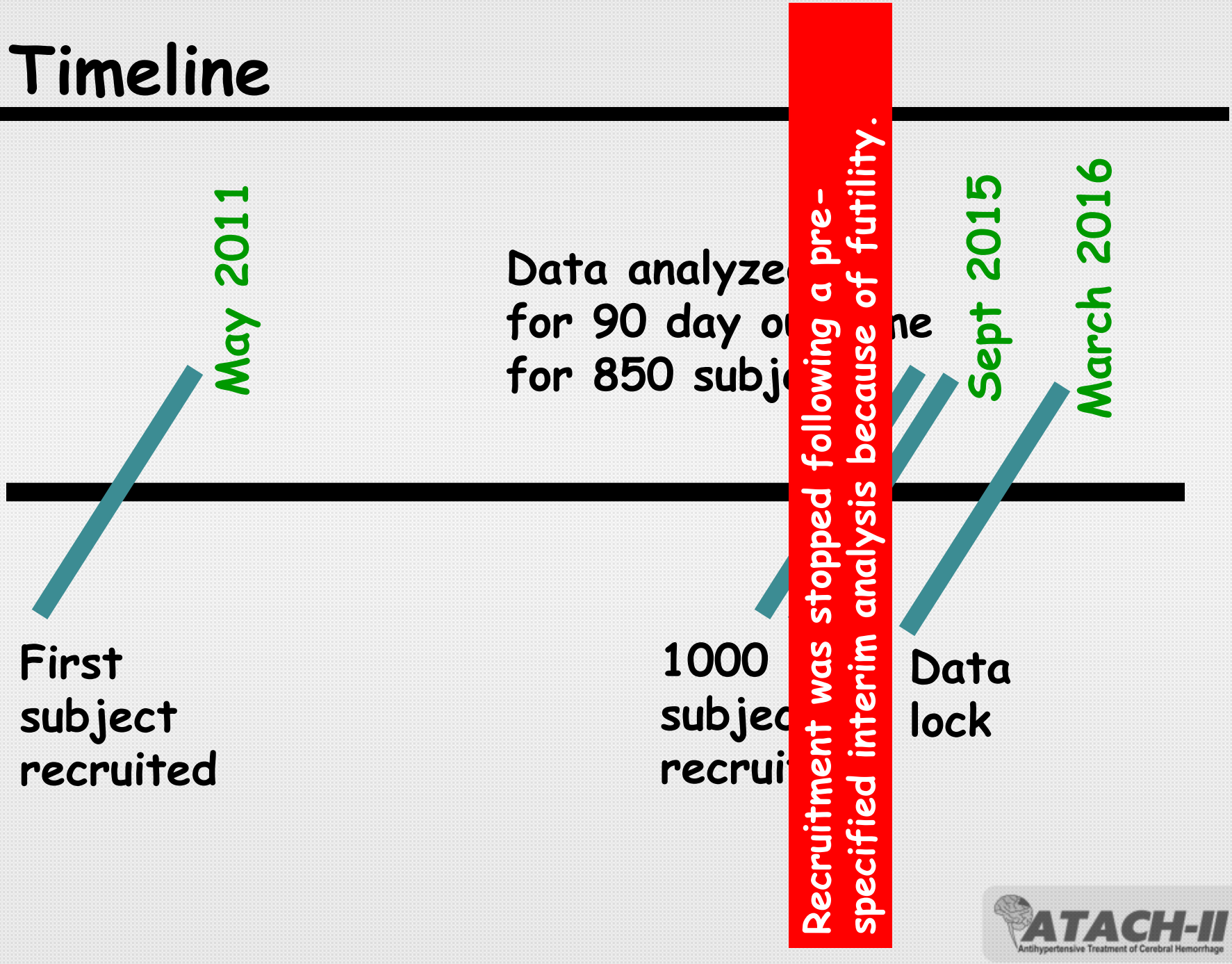
Timeline



Re: Qureshi AI, et al.; N Engl J Med. 2016 Jun 8 [Epub ahead of print]

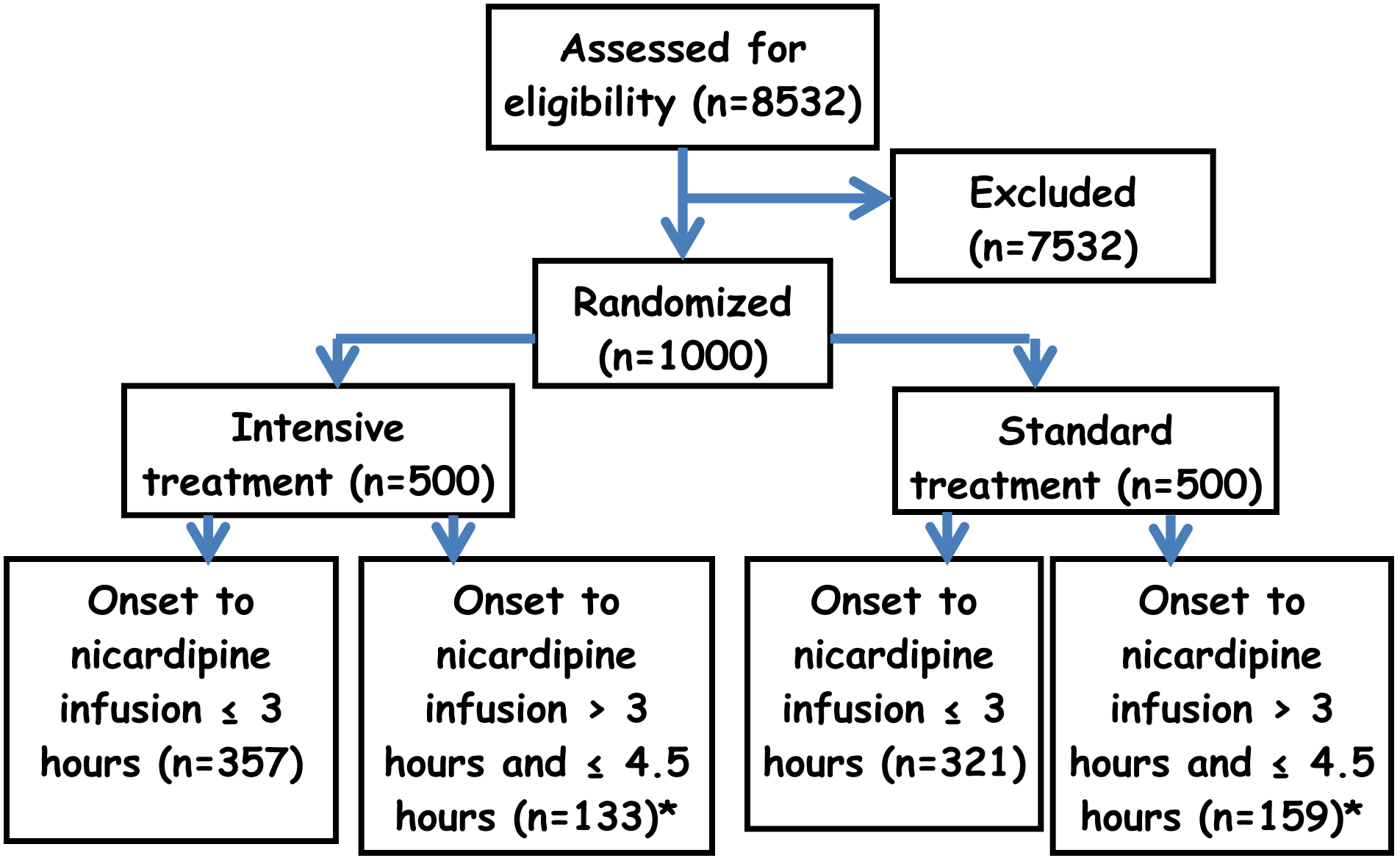
ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

Timeline

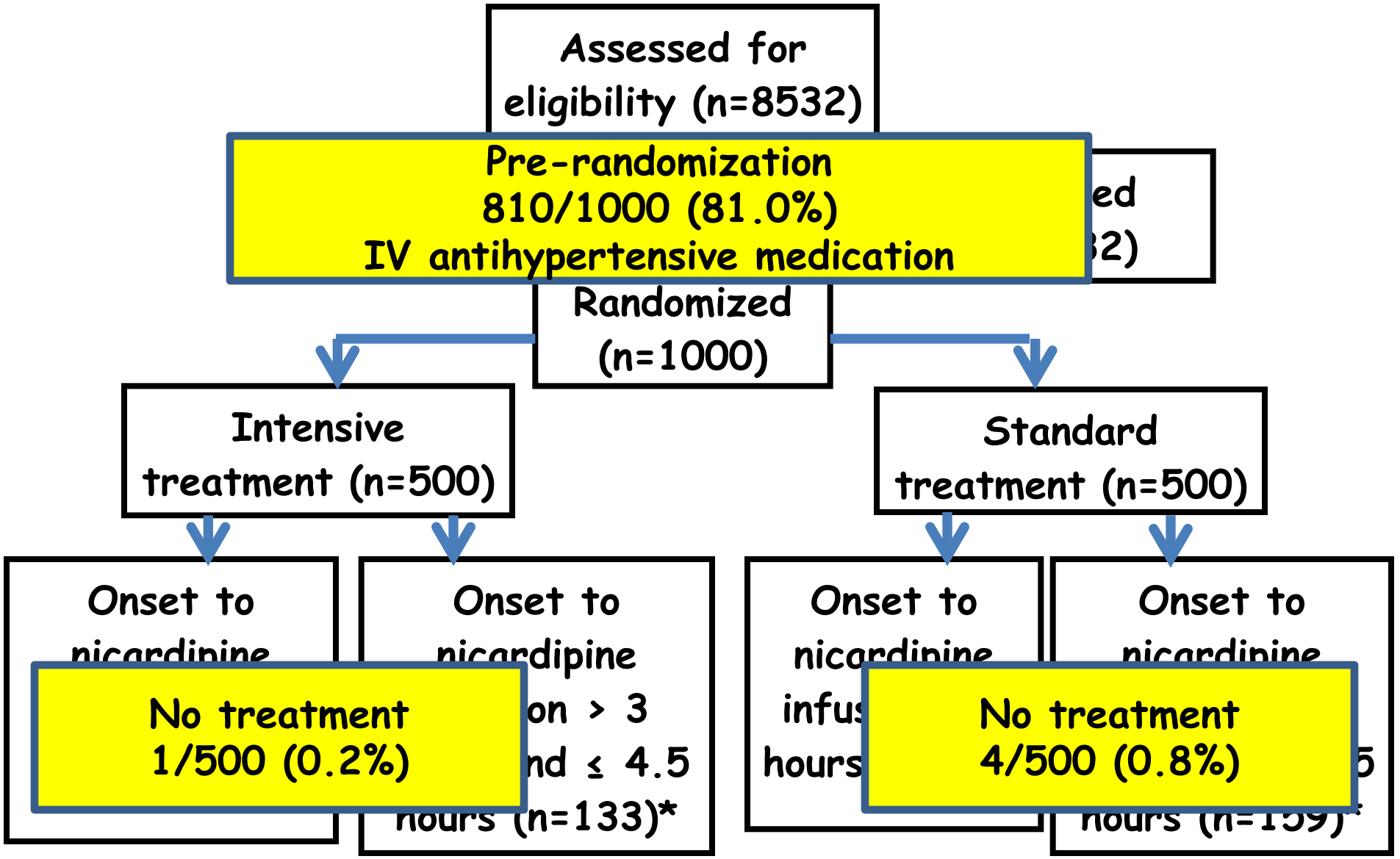


ATACH-II
Antihypertensive Treatment of Cerebral Hemorrhage

The CONSORT Flow diagram to demonstrate progress through the phases of the trial



The CONSORT Flow diagram to demonstrate progress through the phases of the trial



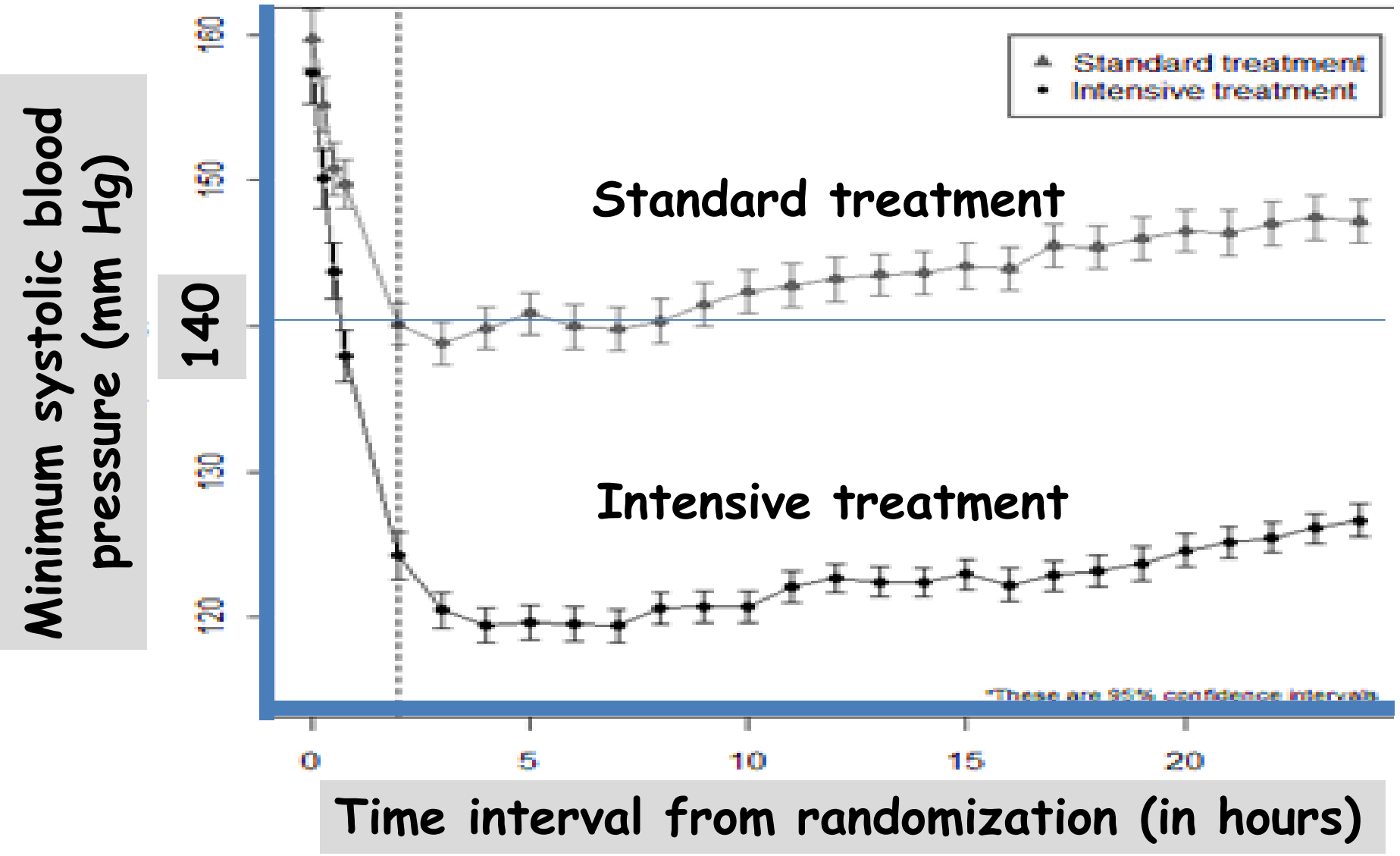
Demographic and clinical characteristics of subjects according to treatment group

Characteristics	Intensive treatment n=500	Standard treatment n=500
Age, year (mean± standard deviation)	62±13.1	61.9±13.1
Glasgow Coma Scale score§ -		
3-11	73/500 (14.6)	74/500 (14.8)
12-14	152/500 (30.4)	142/500 (28.4)
15	275/500 (55)	284/500 (56.8)
Intracerebral hematoma volumet, mm^3 – median (range)	10.3 (2.3-85.2)	10.2 (.98-79.1)

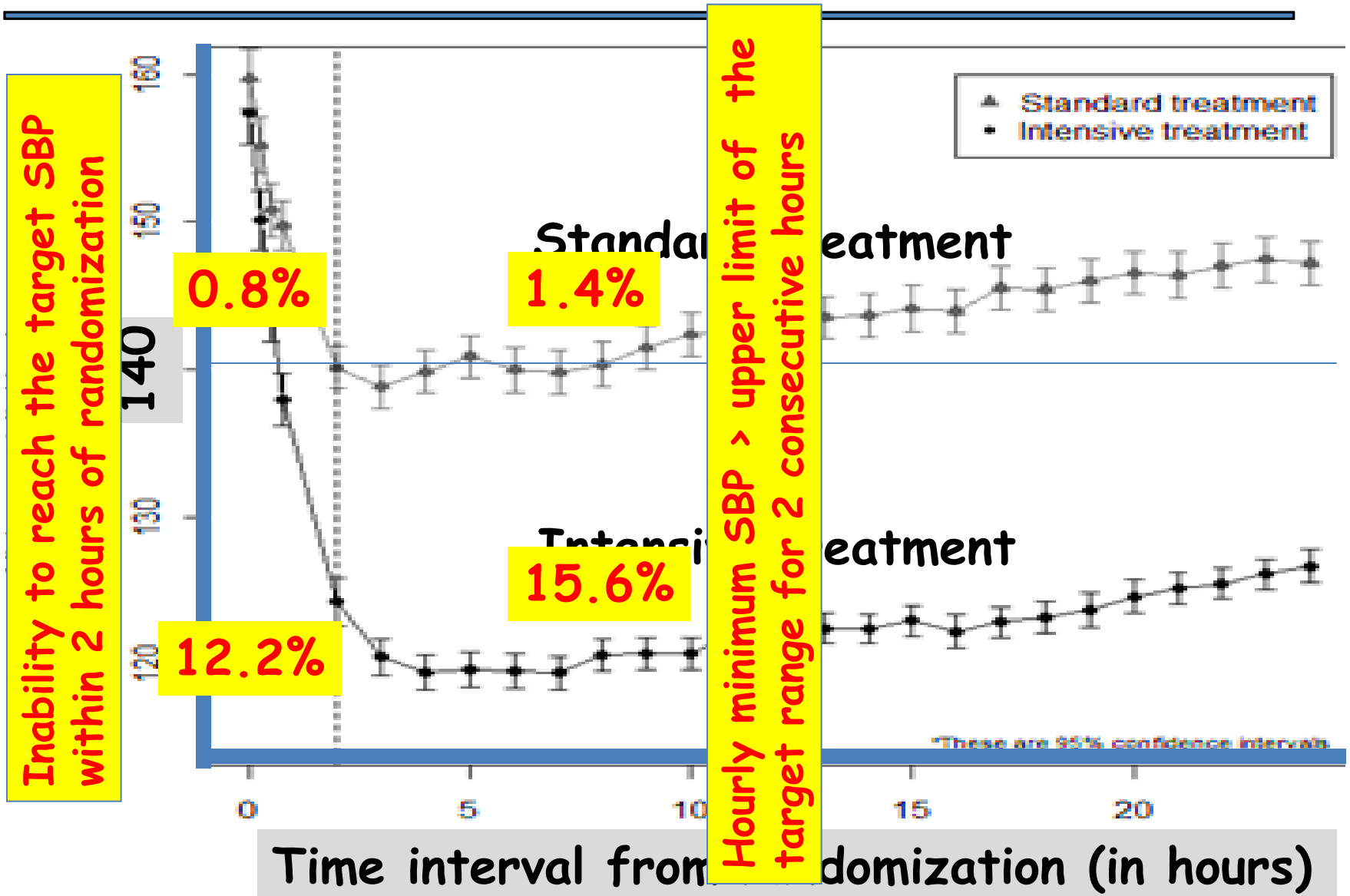
Baseline and treatment characteristics of subjects according to treatment group

Characteristics	Intensive treatment n=500	Standard treatment n=500
Systolic blood pressure at presentation in emergency department*, mmHg (mean± SD)	200±27.1	201.1±26.9
Symptom onset to randomization time, minutes (mean± SD)	182.2±57.2	184.7±56.7
Mean minimum systolic blood pressure, during the first 2 hours post randomization[2], mm Hg - mean ±SD	128.9±16	141.1±14.8

The mean values of hourly minimum systolic blood pressure (with model based 95% CI) for first 24 hours post randomization by treatment group



Primary and secondary treatment failures



Primary outcome: Death or disability (modified Rankin scale 4-6) at 90 days post-randomization

Outcome	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)[1]	Adjusted Relative Risk (95% CI)[1,2]
Death or disability - number/total number observed (%)	186/481 (38.7)	181/480 (37.7)	1.02 (0.83, 1.25) p=0.84	1.04 (0.85,1.27) p=0.72

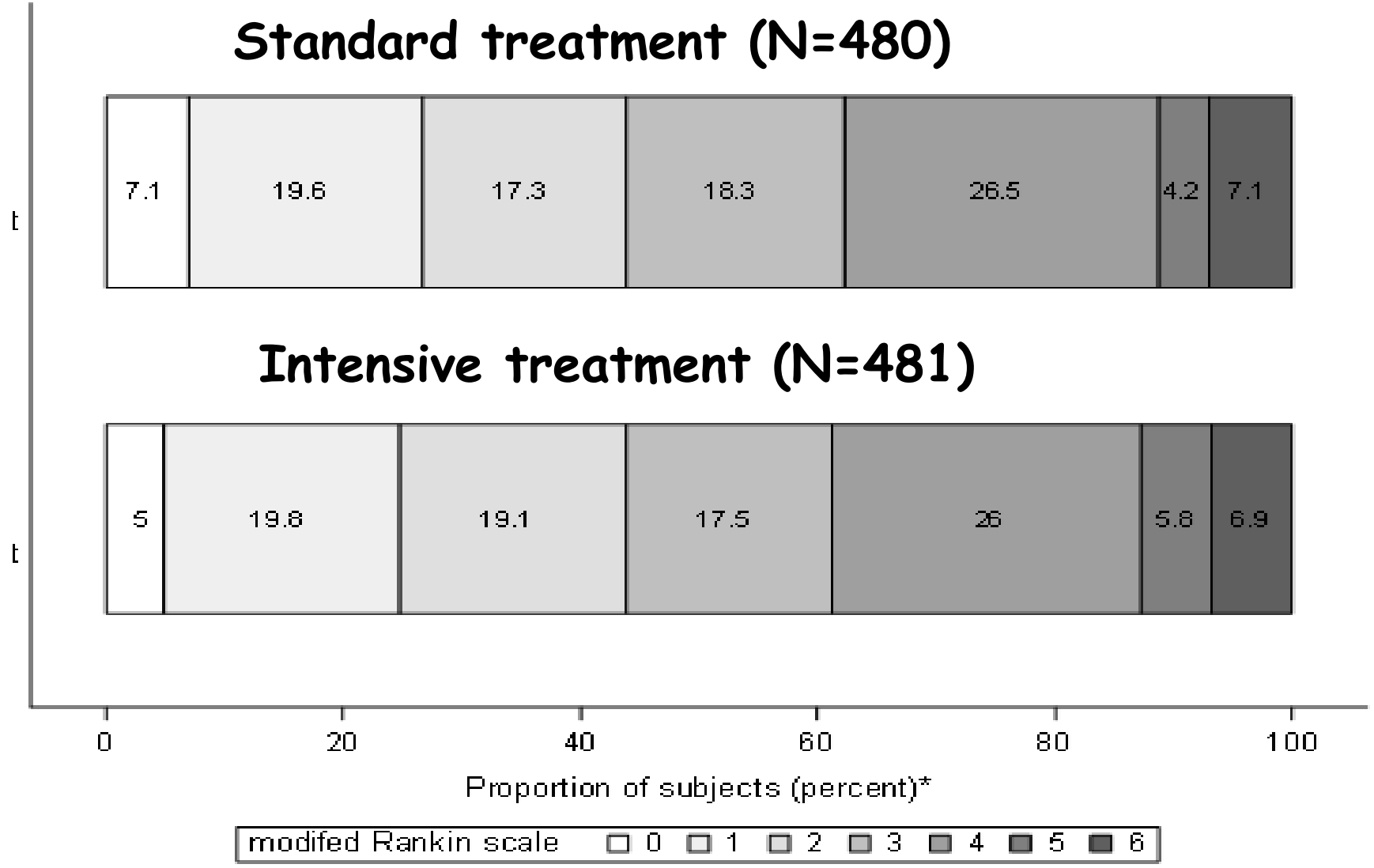
[1]Relative risk for modified Rankin Scale are based on multiple imputation analysis and [2] adjusting for the effects of age, GCS and presence/absence of intraventricular hemorrhage

Primary outcome: Death or disability (modified Rankin scale 4-6) at 90 days post-randomization-worst case scenario analysis

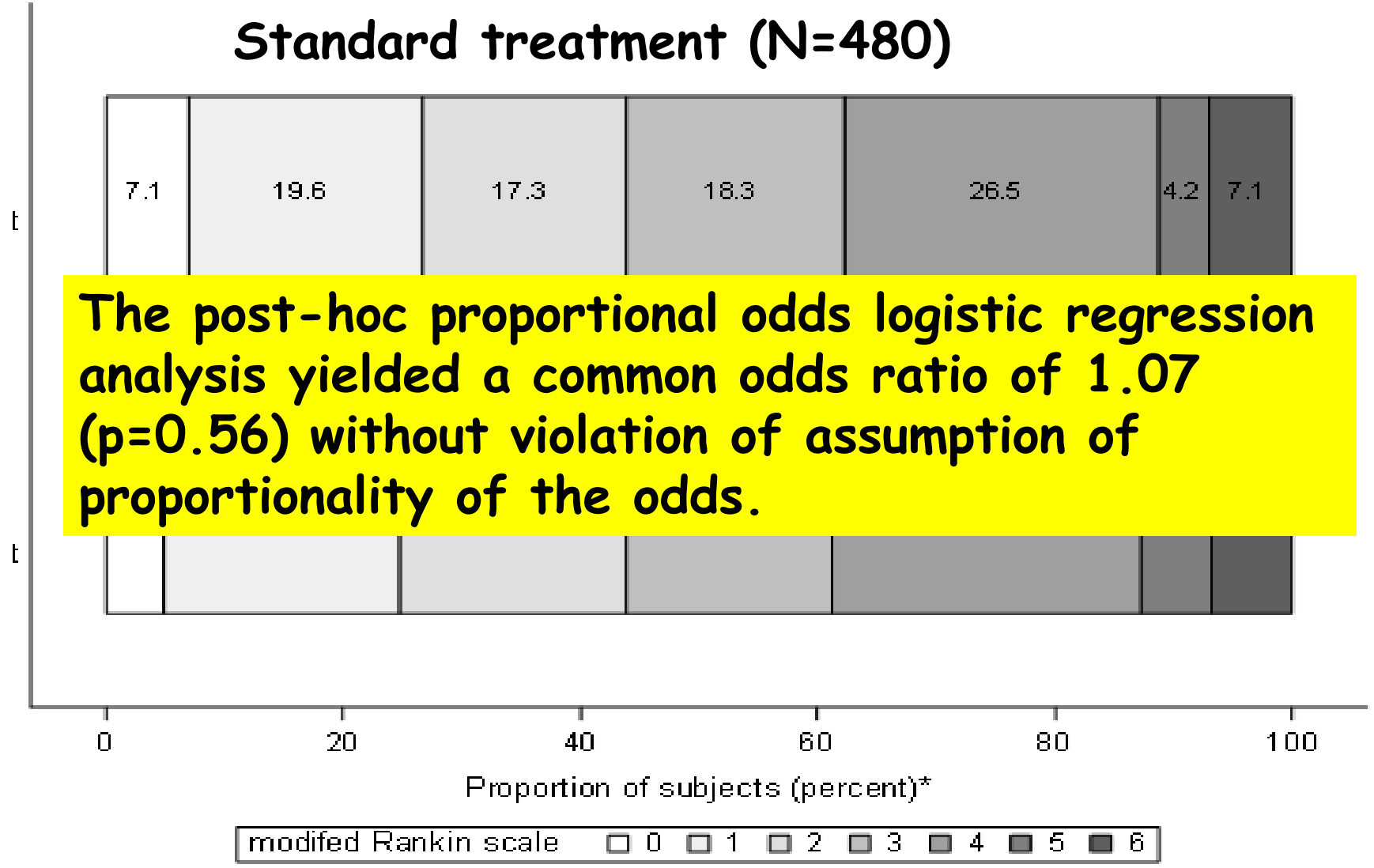
Outcome	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)[1]	Adjusted Relative Risk (95% CI)[1,2]
Death or disability - number/total number observed (%)	205/500 (41)	201/500 (40.2)		1.04 0.85, 1.26

[1]Relative risk or beta estimate (95% CI) for modified Rankin Scale assumes that missing data patients have worst outcome (modified Rankin Scale of 4-6)

Ordinal distribution of mRS at 90 days post-randomization



Ordinal distribution of mRS at 90 days post-randomization



The post-hoc proportional odds logistic regression analysis yielded a common odds ratio of 1.07 (p=0.56) without violation of assumption of proportionality of the odds.

Secondary endpoints among subjects according to treatment group.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Hematoma expansion	85/450 (18.9)	104/426 (24.4)	0.78 (0.59, 1.04) p=0.09	0.78 (0.58, 1.03) P=0.08
Neurologic deterioration within 24 hours	55/500 (11)	40/500 (8)	1.38 (0.92, 2.07) p=0.13	1.39 (0.92, 2.09) p=0.11

Secondary endpoints among subjects according to treatment group.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Treatment-related SAEs within 72 hours	8/500 (1.6)	6/500 (1.2)	1.33 (0.46, 3.84) p=0.59	1.37 (0.47, 3.95) p=0.56
Any SAEs within 3 months	128/500 (25.6)	100/500 (20)	1.28 (0.99, 1.66) p=0.06	1.30 (1.00, 1.69) p=0.05
Hypotension within 72 hours	6/500 (1.2)	3/500 (0.6)	2.00 (0.50, 8.00) p=0.33	1.96 (0.49, 7.87) p=0.34

Secondary endpoints among subjects according to treatment group.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Treatment -rela SAEs withi hours	8/500	6/500	1.33	1.37 95)
Any SAEs within 3 months	128/500 (25.6)	100/500 (20)	1.28 (0.99, 1.66) p=0.06	1.30 (1.00, 1.69) p=0.05
Hypotens-ion within 72 hours	6/500 (1.2)	3/500 (0.6)	2.00 (0.50, 8.00) p=0.33	1.96 (0.49, 7.87) p=0.34

There was a lack of temporal relationship to intervention or aggregation of particular adverse events in any group

Results of analysis performed after grouping the related events (events that represent the same condition of interest by body system) classified using MedDRA terminology terms.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Any renal AE within 7 days	45 (9.0%)	20 (4.0%)	2.25 (1.33,3.81) p= 0.0025	2.32 (1.37,3.94) p= 0.0018
Any cardiac AE within 7 days	57 (11.4%)	42 (8.4%)	1.36 (0.91,2.02) p= 0.1332	1.40 (0.94,2.08) p= 0.1004

Results of analysis performed after grouping the related events (events that represent the same condition of interest by body system) classified using MedDRA terminology terms.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Any renal AE within 7 days	45 (9.0%)	20 (4.0%)	2.25 (1.33,3.81)	2.32 (1.37,3.94)
Any care with days				

The rate of renal adverse events within 7 days after randomization was significantly higher in the intensive-treatment group than in the standard-treatment group

Quality of life endpoints among subjects according to treatment group.

Outcomes	Intensive treatment n=500	Standard treatment n=500	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
EQ-5D Utility Index[7] - Median (Range)	0.7 (-0.1,1.0)	0.7 (0, 1.0)	-0.01 (-0.05, 0.02) p=0.47	-0.02 (-0.05, 0.02) p= 0.29
EQ-5D Visual Analog Scale[8] - Median (Range)	62.5 (0, 100)	70 (0, 100)	-1.14 (-5.28, 2.99) p=0.59	-1.32 (-5.25, 2.60) p=0.51

Discussion

- ATACH-2 was discontinued for futility prior to reaching target enrollment of 1,280. The absolute difference in rates of death and disability between the two groups was 1%.

- The study was powered to identify a 10% or greater absolute risk reduction with intensive treatment as smaller risk reduction was expected to be viewed as insufficient for broad acceptance of a new intervention.

Re: Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon BW; N Engl J Med. 2016 Jun 8 [Epub ahead of print]

Discussion

- The observed rate (37.7%) of death or disability at 3 months was lower than the rates (60%) anticipated in trial design based on previous literature.
  - A high proportion of patients with favorable baseline characteristics (e.g., 56% with baseline GCS score of 15).
  - Standardizing overall medical management by independent oversight committee.
  - Low rate of withdrawal of care (0.4% withdrawal of care related deaths)-34% in routine practice.

- Incorporated the pre-randomization use of IV antihypertensive agents to ensure timely compliance with existing guidelines but may have obscured the effectiveness of trial intervention.

Conclusions

- Compared to a target systolic blood pressure of 140-179 mmHg, treating subjects with intracerebral hemorrhage to a target systolic blood pressure of 110-139 mmHg did not lower the rate of death or disability at 3 months after symptom onset.

Re: Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon BW; N Engl J Med. 2016 Jun 8 [Epub ahead of print]

Thank you

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2 trial investigators' meeting, Honolulu, Hawaii, April 26th, 2016