SYMPTOMATIC INTRACRANIAL HEMORRHAGE IN THE ALIAS MULTICENTER TRIAL: RELATIONSHIP TO ENDOVASCULAR THROMBOLYTIC THERAPY

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Abstract

Background—In the ALIAS Part 2 Multicenter Trial, 85% of subjects received standard-of-care intravenous tPA, and 21% received some form of endovascular thrombolysis. The overall rate of symptomatic intracranial hemorrhage was within the expected range but was higher in albumin- than in saline-treated subjects.

Aims and Methods—Using the trial's Public Use Dataset, we analyzed factors contributing to symptomatic (sICH) and asymptomatic intracranial hemorrhage in the "safety sample" of 830 subjects.

Results—Four hundred sixteen subjects received ALB therapy, and 414 received saline. Intravenous tPA was given to 68.2%; IV tPA plus endovascular intervention in 16.4%; and endovascular therapy alone in 4.3%. sICH occurred in 41 subjects – within the first 12 hours in one-third of cases, and within the first day in ~60%. Intravenous tPA had been used in 78% of sICH subjects – no higher than in the overall cohort. In contrast, 48.8% of subjects with sICH had received *endovascular* therapy – markedly higher than the 20.7% rate in the entire cohort (p=0.0001). 68.3% of subjects with sICH had received ALB, and 31.7% saline (risk ratio 2.14, p=0.025). Other factors associated with sICH were baseline NIHSS and ASPECTS scores and the SEDAN score. 41.4% of subjects with sICH died. The odds ratio (OR) for sICH was 3.89 (95% CI 2.04–7.41) with endovascular therapy and 2.15 (CI 1.08–4.25) with albumin.

Conclusions—Endovascular thrombolysis was the major factor predisposing to sICH, and albumin contributed to this predisposition. The latter may be mediated by albumin's influence on platelet aggregation or collateral perfusion.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Identifier, NCT00235495

Keywords

intracranial hemorrhage; ischemic stroke; albumin; endovascular therapy; thrombolysis; neuroprotection

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The ALIAS (Albumin in Acute Stroke) Part 2 multicenter clinical trial was a phase III, randomized placebo-controlled investigation to determine whether the early administration of high-dose human albumin would improve the neurological and functional outcome of patients with acute ischemic stroke. As presented in the primary report of the trial's results,[1] no overall clinical benefit was demonstrated. Standard-of-care intravenous thrombolytic therapy with tPA (alteplase) was administered to 712 (85%) of the 841 subjects in the intent-to-treat population; and 176 subjects (21%) received some form of endovascular thrombolytic intervention (mechanical and/or drug). As the trial progressed to Part 2,[2] endovascular stroke therapy was provided to an increasing proportion of stroke patients as part of routine care. This was permitted by the trial's protocol and was a concurrent secular evolution in acute stroke treatment.

As albumin has properties potentially useful in preventing reperfusion injury, we suspected that ALB therapy might reduce sICH.[3] Although the overall rate of symptomatic intracranial hemorrhage (sICH) within 24 hours of randomization (2.9%) was within the clinically acceptable range,[4] it was unexpectedly more frequent in subjects treated with albumin (ALB) than with saline-placebo (SAL) (relative risk 2.42, 95% CI 1.02–5.78). In this report, we present a detailed analysis of both symptomatic and asymptomatic ICH in the ALIAS Part 2 trial and explore contributory factors.

METHODS

The details of the trial's design, inclusion and exclusion criteria, and outcomes have been reported previously.[1] In brief, subjects aged 18 through 83 with baseline National Institutes of Health Stroke Scale (NIHSS) scores of 6 or greater were randomized 1:1 to treatment with either 25% albumin (ALB, 2 g/kg) or a comparable volume of isotonic saline (SAL) started within 5 hours of stroke onset. Exclusions were chiefly cardiovascular in nature. A favorable primary outcome was defined as a score of 0 or 1 on either the NIHSS or the modified Rankin Scale (mRS), or both, at 90 days post-randomization. The present analysis was conducted on the protocol-defined "safety sample" of 830 subjects who had received at least 20% of the weight-based study-drug dose. The data were derived from the trial's Public Use Dataset.

In univariate analyses, we compared baseline and treatment-related factors hypothesized to be possibly contributory to sICH development: age, baseline NIHSS score, baseline plasma glucose, study drug (ALB or SAL), use of IV tPA, use of endovascular thrombolysis, baseline ASPECTS score, and presence of hyperdense MCA sign on baseline neuroimaging. We used the Mann-Whitney rank sum test and chi-square or Fisher's exact test as appropriate. We also considered the SEDAN score to estimate the extent of sICH risk in patients receiving IV thrombolysis;[5, 6] this score was derived 974 ischemic stroke patients and validated in another >800 subjects but did not include patients with endovascular therapy.[6] The SEDAN score ranges from 0 to 6 and incorporates blood glucose level, early ischemic signs and hyperdense cerebral artery sign on admission CT scan, age > 75 years, and NIHSS score of 10 or above. In the analysis of Strbian et al,[6] a SEDAN score of 3 would predict a sICH rate of ~11%.

We derived a multivariable model using logistic regression to obtain an adjusted estimate of effect size. Within this model we assessed the possible interaction of ALB and endovascular treatment, after adjusting for the prognostic variables listed above. Significance was assessed at the p<0.05 level. Statistical analyses utilized IBM SPSS Statistics, version 22; and SigmaPlot for Windows, version 11.0.

RESULTS

The baseline and treatment characteristics of the entire safety cohort are presented in Appendix Table 1. A total of 416 subjects received ALB, and 414 received SAL (placebo). Mean age was 64; median baseline NIHSS score was 10–11; and the median interval from stroke onset to initiation of study drug was 199 min. Intravenous tPA was administered to 566 subjects (68.2%); IV tPA plus an endovascular intervention in 136 (16.4%); and endovascular therapy alone in 36 (4.3%). The remaining 92 subjects (11.1%) received no thrombolytic treatment. Intravenous tPA therapy was begun, on average, 52 ± 24 (SD) min prior to randomization and 135 ± 48 min following stroke onset.

Symptomatic Intracranial Hemorrhage (sICH)

Treatment-related symptomatic ICH (sICH) was defined per-protocol as intracranial hemorrhage proven by neuroimaging and associated with deterioration in neurological status; the site investigator must have adjudicated the ICH to be the primary cause of the subject's deterioration. sICH occurred in 41 subjects, whose clinical features are presented in Table 1. The mean age was 68 ± 9 (SD) years; median baseline NIHSS was 15. These values were both somewhat higher than for the safety cohort as a whole.

Thirty-five subjects with sICH, and 698 without sICH, had received some form of thrombolytic therapy (IV tPA and/or endovascular) (p=0.62, Fisher exact test). *Intravenous* tPA had been administered to 32 subjects, or 78% - no more than for the entire safety cohort. In contrast, 20 of the 41 subjects (48.8%) with sICH had received some form of *endovascular* thrombolysis – a percentage markedly higher than the 20.7% in the entire safety cohort (p=0.0001, Fisher exact test). Twenty-eight subjects with sICH (68.3%) had received ALB, and 13 (31.7%) had received SAL (risk ratio, 2.14; p=0.025, Fisher exact test).

As shown in Table 1, ~60% of all sICH events occurred within the first day following randomization; one-third of cases within the first 12 hours; and only 7 of 41 occurred after day 8. Endovascular thrombolysis had been employed in 11 of the 16 cases with onset within the first half-day, and death resulted in 10 of these subjects. Overall, the median time from randomization to sICH onset was 0.9 days (interquartile range, 0.3–1.8 days), and the overall rate of death was 41.4%. Only rarely did subjects with early sICH (defined as sICH onset < day 8) attain a favorable primary outcome (3 of 34 subjects, or 9%) (Table 1).

Table 2 compares descriptive variables in subjects with vs. without early sICH (i.e., onset < day 8). The following factors were associated with early sICH: baseline NIHSS score (p=0.025); baseline ASPECTS (p=0.005); SEDAN score (p=0.011); and use of *endovascular* thrombolytic therapies (p<0.0001). ALB therapy (p=0.053) and age (p=0.057)

were of borderline significance in these univariate analyses. Use of *intravenous* tPA, intervals from stroke onset to randomization and to start of thrombolytic therapies, gender, baseline glucose, and order of randomization into the trial were not associated with a propensity to early sICH. Failure to achieve a favorable primary outcome, and likelihood of death, were markedly increased in subjects with early sICH (p<0.0001).

Using binary logistic regression, we derived adjusted estimates of the effect of endovascular therapy on early sICH (onset < day 8) and on any sICH; we accounted for IV tPA treatment, drug (ALB, SAL), age, baseline NIHSS score (bNIHSS), and the possibility of multiplicative interaction of endovascular therapy and drug. IV tPA and bNIHSS did not influence the model. Table 3 shows these analyses. Endovascular therapy was a strong predictor of both early sICH (odds ratio 5.94; CI 2.9–12.1) and any sICH (OR 3.98; 2.0–7.4) (p<0.001). ALB therapy increased the odds of both early sICH and any sICH by ~2-fold in this model but was significant only for the latter. Older age increased the odds of sICH to a significant but minor degree (OR 1.03–1.04) (Table 3). There was no demonstrable interaction of endovascular therapy and study drug.

In additional analyses, we categorized thrombolytic interventions according to the four combinations used in the trial (i.e., IV tPA alone; IV tPA plus endovascular therapy [mechanical and/or intra-arterial tPA]; endovascular therapy alone; and neither IV nor endovascular therapy), and we explored the relationship of each of these to study drug (ALB or SAL) (Figure 1). Among the 41 subjects with sICH, chi-square analysis revealed highly significant differences of sICH in subjects receiving endovascular therapy; and, in particular, when endovascular therapy was used in conjunction with ALB ($\chi^2 = 26.9$, 7 df, p=0.0004). Separate analyses of sICH subjects receiving ALB vs. SAL (corrected for multiple comparisons) revealed significant sICH differences from expected levels associated with endovascular therapy in ALB subjects (p<0.001), but not in SAL subjects (p=0.13).

Asymptomatic Intracranial Hemorrhage (asx-ICH)

Clinically asymptomatic ICH (asx-ICH) was detected by neuroimaging in 81 subjects. Seventy-six subjects with asx-ICH, and 657 without asx-ICH, had received some form of thrombolytic therapy (IV tPA and/or endovascular) (p=0.14, Fisher exact test). Mann-Whitney rank sum tests revealed that asx-ICH was significantly associated with the following factors: baseline NIHSS score (p<0.001); baseline ASPECTS (p<0.001); use of endovascular therapy (p=0.003); and SEDAN score (p<0.001). Median bNIHSS was 14 (IQR, 10–19) in asx-ICH subjects and 11 (IQR 8–16.5) in subjects without asx-ICH. Age, study drug (ALB, SAL), and IV tPA use were not associated with asx-ICH development.

Chi-square analysis was used to assess asx-ICH in relation to thrombolytic interventions and study drug in a manner similar to that described above for sICH. This also revealed significant differences chiefly attributable to the use of endovascular therapy (Figure 1) ($\chi^2 = 15.2$, 7 df, p=0.034). Separate analyses of asx-ICH subjects receiving ALB vs. SAL revealed that this trend was attributable to endovascular therapy in ALB subjects (p=0.034), but not in SAL subjects (p=0.089) (Figure 1).

DISCUSSION

These results show that endovascular thrombolytic therapies in the ALIAS Part 2 Trial constituted the major risk factor for the development of symptomatic intracranial hemorrhage (sICH); that the majority of these sICH cases developed within 12–24 hours of randomization (Table 1); and that treatment with ALB accentuated the predisposition to sICH development (Table 3; Figure 1).

While there is abundant published information as to the risk of sICH following *intravenous* thrombolysis, fewer data are available for endovascular therapy (with or without IV tPA). In a comprehensive survey of sICH following IV thrombolysis for ischemic stroke, Seet and Rabinstein[4] compiled data from 7 randomized controlled trials, 7 stroke registries and 10 cohort studies. Overall, mean age was 69 years; baseline NIHSS was 12.5 (range 9–15); sICH incidence was $5.6 \pm 2.3\%$; and mortality $14.7 \pm 4.8\%$. In the 7 major randomized controlled trials of IV tPA (N=2124) – in which sICH definitions differed as to interval from treatment, extent of neurological decline, and neuroimaging criteria -- mean sICH rate was $7.5 \pm 1.5\%$, and mortality $15.7 \pm 6.9\%$.[4] The criteria for sICH used in the ALIAS Trial most closely resembled those of the 1995 NINDS multicenter trial of IV tPA – i.e., neuroimaging-proven hemorrhage associated in the investigator's judgment with neurological worsening within 36h following IV thrombolysis.[7] In the 7 summarized reports utilizing the NINDS criteria, the mean sICH rate was $7.61 \pm 0.94\%$.[4]

It is more difficult to form a unitary concept of hemorrhagic complications following *endovascular* therapy for stroke, particularly in view of the evolution of improved mechanical endovascular devices over the past decade. The early Merci device had a 7.8% sICH rate;[8] and the MultiMERCI trial, utilizing an improved retriever within 8 hours after initial IV tPA therapy, reported a 9.8% sICH rate.[9] In the multicenter SWIFT trial, in which the Merci retriever was compared to the newer Solitaire device (the latter not reportedly used in ALIAS), the respective sICH rates differed markedly -- 10.9% for Merci vs. 1.7% for Solitaire.[10] Correspondingly, the odds ratio for successful recanalization with Solitaire compared to Merci was >5. The Penumbra device was associated with a 10% sICH rate.[11] Reports of the combined use of IV tPA and endovascular therapy, in general, note incidences of sICH comparable to IV tPA alone.[12] In the landmark Interventional Management of Stroke (IMS) III multicenter trial comparing IV plus endovascular therapy with IV therapy alone, sICH rates within 30 hours were similar for the two treatments (6.2% and 5.9%, respectively), as were outcomes.[13] In a meta-analysis of 5 randomized trials comparing endovascular therapy (with or without IV tPA) to standard-of-care IV tPA alone, sICH rates did not differ by treatment modality (risk ratio 0.99), and the analysis failed to show superiority of endovascular therapy over IV tPA.[14]

In the ALIAS Part 2 Trial, the overall sICH rate within 24 hours in both the intent-to-treat analysis[1] and the safety cohort was 2.9% -- thus, as low as or lower than in other reported thrombolytic trials (see above). Nonetheless, this rate differed significantly by treatment: 4.1% in ALB-treated subjects vs. 1.7% with SAL (relative risk, 2.42, 95% CI 1.02–5.78).[1] In a recent review, Jickling et al[15] comprehensively surveyed the factors associated with hemorrhagic transformation after ischemic stroke in experimental and clinical studies. A

factor of possible relevance to ALIAS relates to the use of antiplatelet agents in close temporal relationship to tPA treatment.[16, 17] This is pertinent in that several studies indicate that albumin may exert a platelet anti-aggregatory effect. Under conditions of thromboxane synthase inhibition, serum albumin enhances the impairment of platelet aggregation by increasing the formation of the anti-aggregatory prostaglandin, PGD2.[18] Local concentrations of albumin exert a profound influence on the potency of endogenously released platelet-activating factor (PAF).[19] Albumin also exerts a dose-dependent role in preventing histone-induced platelet aggregation.[20] In ex-vivo studies of canine carotid arteries, albumin pretreatment significantly reduced platelet and red cell deposition on damaged arteries.[21] Albumin-coating of extracorporeal pump tubing reduced platelet adherence.[22]

The status of the collateral circulation is also relevant to hemorrhagic transformation after ischemic stroke.[15] Poor collaterals are associated with larger infarcts and worse functional outcome,[23] and, in the setting of recanalization, they confer an increased risk of hemorrhagic transformation.[24, 25] Bang et al[26, 27] reported a 2-center study of >200 acute ischemic stroke patients receiving endovascular therapy, in whom there was a 19% rate of symptomatic hemorrhagic transformation. When revascularization was achieved, patients with poorer collateral grade on baseline angiography were more likely to undergo sICH (odds ratio, 2.7, 95% CI 1.2–6.1)[26] as well as a lower rate of complete revascularization and greater infarct growth.[27]

The ALIAS trials were not designed to assess the status of the collateral circulation. Several experimental studies from our group, however, indicate that high-dose albumin administration in focal cerebral ischemia influences cerebral blood flow (CBF) and collateral perfusion. In autoradiographic studies of temporary MCA occlusion, high-dose ALB improved perfusion to regions of critically reduced local CBF.[28] In a model of permanent MCA occlusion, high-dose ALB also increased cortical perfusion.[29] In a confocal microscopic study of rats with reversible MCA occlusion, ALB therapy increased post-ischemic microvascular perfusion and was associated with the partial clearance of adherent thrombotic material from cortical venules.[30] In vivo studies employing two-photon laser-scanning microscopy demonstrated that ALB (but not saline) reversed impaired microvascular flow velocity distal to a laser-induced arteriolar thrombus[31] and augmented the effect of sub-lytic doses of reteplase in this model.[32]

Definitive evidence of ALB's effect on collateral perfusion was obtained in a study utilizing two inbred mouse strains that differed in their degree of collateral circulation, and in which cortical perfusion was studied by in vivo laser speckle contrast flow imaging following distal MCA occlusion.[33] In the BALB/c mouse strain, which has sparse brain collaterals, ALB treatment (but not SAL) enhanced perfusion by ~2-fold in both the ischemic-core and penumbral regions, while in the better-collateralized CD-1 strain, this effect was not present.

Based on the above considerations, we suggest that ALB therapy in the ALIAS Part 2 Trial may have induced an "unwanted" enhancement of collateral perfusion in subjects with poor baseline collateralization such that, when some degree of recanalization was then induced by endovascular therapy, ALB may have enhanced the propensity to sICH and poor outcome.

This hypothesis would be amenable to clinical investigation by employing sequential neurovascular imaging in relation to ALB or saline therapy.

Acknowledgments

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Symptomatic Intracranial Hemorrhage

Asymptomatic Intracranial Hemorrhage
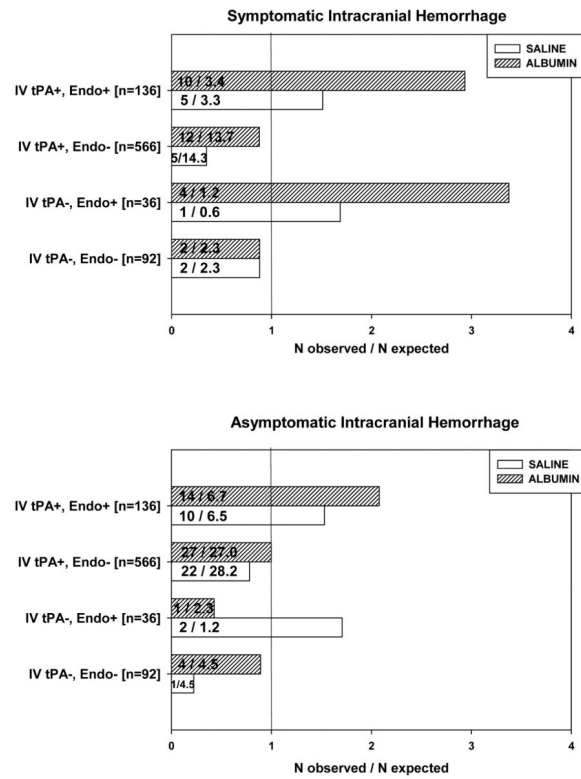
Figure 1.
Results of chi-square analysis of symptomatic (upper panel) and asymptomatic (lower panel) intracranial hemorrhage by treatment (ALB, saline) in the 4 categories of thrombolytic interventions employed in the ALIAS Part 2 Trial (IV tPA plus endovascular therapy; IV tPA without endovascular; endovascular without IV tPA; and neither therapy). The fractions shown represent (number of observed cases)/(number of expected cases based upon the proportion of the respective thrombolytic category within the entire sample). Observed numbers of symptomatic ICH (sICH) cases significantly exceed expected numbers in subjects receiving endovascular therapies together with ALB. (See text for statistical details.)

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Table 1

Characteristics of subjects with symptomatic Intracranial hemorrhage

Sub-ject	Day of sICH Onset	Age	Gen-der	bNIHSS	Baseline ASPECTS	Treat-ment	IV tPA	Endo-vascular: Mechan-ical Device	Endo-vascular: Intra-arterial tPA	NETT site	90-day NIHSS	90-day mRS	Favorable Primary Outcome	Death	Day of Death	SEDAN score	Notes
1	0.1	81	F	9	6	ALB	X	X	X	x				X	9	3	*b,c*
2	0.1	74	F	8	10	ALB		X	X		3	1	X			2	*d*
3	0.1	65	M	18		ALB	X		X	x				X	2	1	
4	0.2	65	M	22	9	ALB	X	X				4				3	*c*
5	0.2	56	M	7	10	ALB		X	X	x				X	7	2	*a,c,d,f*
6	0.2	63	F	10	8	ALB	X	X	X					X	1	1	*b*
7	0.2	79	M	11	8	SAL		X						X	8	4	*b*
8	0.2	69	F	17	10	SAL	X	X	X					X	1	3	*a,d*
9	0.3	72	M	7	9	ALB		X		x				X	9	2	*b,c*
10	0.3	60	M	15	7	SAL	X	X	X		3	2				4	*d*
11	0.3	66	M	9	10	ALB	X			x	19	5				3	
12	0.4	51	F	15	10	ALB	X	X						X	1	2	*c,d*
13	0.4	52	M	11	9	ALB	X				8	4				2	
14	0.5	55	M	17	8	ALB	X			x	20	4				3	
15	0.5	79	F	20	8	ALB	X							X	2	5	
16	0.5	65	F	16	4	ALB	X			x				X	6	2	
17	0.7	72	M	8	9	SAL	X			x				X	68	2	
18	0.7	75	F	15	6	SAL	X	X		x	17	4				3	*c*
19	0.8	52	M	9	8	ALB	X	X	X	x	7	3				1	*c*
20	0.9	61	F	15	10	SAL	X				1	2	X			2	
21	0.9	64	F	10	8	ALB	X			x	13	4				3	
22	0.9	65	M	29	8	ALB				x		3				2	
23	0.9	81	F	10	7	ALB	X				8	3		X	154	3	
24	1	78	M	10	9	SAL	X			x	5	1	X			3	

Subject	Day of sICH Onset	Age	Gender	bNIHSS	Baseline ASPECTS	Treatment	IV tPA	Endovascular: Mechanical Device	Endovascular: Intra-arterial tPA	NETT site	90-day NIHSS	90-day mRS	Favorable Primary Outcome	Death	Day of Death	SEDAN score	Notes
25	1	65	F	27	7	ALB	X	X		x	9	4				3	b
26	1.1	72	F	23	7	SAL	X	X		x	11	3				3	a,c
27	1.2	78	F	21	9	SAL	X							X	9	4	
28	1.2	71	M	12	9	ALB	X	X			4	2				3	d
29	1.6	67	M	6	9	ALB	X	X						X	8	2	e
30	1.7	74	M	17	8	ALB	X							X	3	3	
31	1.8	75	M	15	8	SAL	X				11	3				2	
32	2.1	76	F	21	8	ALB	X		X					X	7	3	
33	3.5	79	F	25	5	ALB		X		x				X	16	4	c
34	7.9	80	M	20	10	SAL	X	X		x	9	4				3	b
35	17.3	48	M	7	10	ALB	X				1	2	X			3	
36	19	73	F	11	8	ALB	X				4	4				3	
37	35.3	74	M	6	10	ALB	X			x	3	1	X			1	
38	46.3	77	F	22	3	ALB	X			x	22	4				4	
39	59.7	60	M	19	6	ALB				x	10	4				4	
40	131.1	68	F	9	8	SAL					0	2	X			2	
41	161.3	59	M	24	10	SAL					11	3				2	

bNIHSS, baseline NIHSS score; ALB, albumin; SAL, saline-placebo; NETT, Neurological Emergencies Treatment Trials consortium; mRS, modified Rankin Scale score

Notes:

[a] balloon angioplasty

[b] Concentric device

[c] Penumbra device

[d] Intracranial stent

[e] Eptifibitide

[f] Abciximab

Table 2

Comparison of subjects with and without early sICH (onset < day 8).

Numerical Descriptors	Early sICH (onset < day 8)			No early sICH			p value [*]
	Median	Interquartile range		Median	Interquartile range		
Age (years)	70.0	63.8	76.5	65.5	54.4	75.0	0.057
Baseline NIHSS score	15.0	9.8	20.0	11.0	8.0	17.0	0.025
Baseline ASPECTS	8.0	7.5	9.0	10.0	8.0	10.0	0.005
Baseline Plasma Glucose (mmol/L)	6.4	5.6	6.9	6.5	5.7	7.8	0.378
SEDAN score	3.0	2.0	3.0	2.0	1.0	3.0	0.011
Interval from stroke onset to randomization (min)	179	150	248	190	155	235	0.988
Interval from stroke onset to start of IV tPA (min)	114	91	176	129	98	167	0.522
Interval from stroke onset to start of endovascular therapy [†]	256	166	308	248	196	304	0.903
Order of randomization into trial	472	151	655	423	215	633	0.803
Dichotomous Descriptors	[yes]	[no]		[yes]	[no]		p value [**]
Male gender	18	16		434	362		0.862
Use of IV tPA	28	6		674	122		0.634
Use of endovascular therapy	20	14		152	644		<0.0001
Received albumin	23	11		393	403		0.053
Favorable primary outcome at 90 days	3	31		370	426		<0.0001
Death	17	17		97	659		<0.0001

Notes:

[*] Mann-Whitney rank sum test

[**] Fisher exact test

[†] For endovascular subjects receiving both intra-arterial tPA and a mechanical device, start-time refers to the last-employed modality

Table 3

Binary logistic regression – symptomatic intracranial hemorrhage

Early sICH (onset < day 8)

	Coefficient	S.E.	Wald statistic	P =	Odds Ratio	95% CI – lower bound	95% CI -- upper bound
Any endovascular therapy	1.782	04.364	24.0	<0.001	5.94	2.91	12.12
Drug (ALB, Sal)	0.697	0.382	3.3	0.068	2.01	0.95	4.24
Age	0.035	0.016	4.6	0.031	1.04	1.00	1.07

Any sICH

	Coefficient	S.E.	Wald statistic	P =	Odds Ratio	95% CI – lower bound	95% CI -- upper bound
Any endovascular therapy	1.358	0.329	17.1	<0.001	3.89	2.04	7.41
Drug (ALB, Sal)	0.764	0.348	4.8	0.028	2.15	1.08	4.25
Age	0.030	0.014	4.5	0.035	1.03	1.00	1.06

Appendix Table 1

Baseline and Treatment Characteristics of the Subjects in Safety Sample[*]

	Albumin (N=416)	Saline Control (N=414)
Demographics		
Age (mean, SD)	63.5 (12.9)	64.9 (12.9)
Sex, male (%, n)	52.9% (220)	56.0% (232)
Caucasian (%, n)	74.5% (310)	72.8% (302)
Black (%, n)	16.1% (67)	20.3% (83)
Asian (%, n)	6.0% (25)	4.8% (20)
Medical History		
Hypertension	71.9% (299)	70.5% (292)
Atrial fibrillation	18.8% (78)	18.6% (77)
Past congestive heart failure	4.1% (17)	6.3% (26)
Past myocardial infarction	10.6% (44)	12.1% (50)
Past stroke	20.9% (87)	18.6% (77)
Past transient ischemic attack	12.3% (51)	11.8% (49)
Diabetes mellitus	18.5% (77)	22.5% (93)
Hyperlipidemia	46.6% (194)	51.0% (211)
Peripheral vascular disease	5.0% (21)	6.0% (25)
Clinical Factors		
NIHSS score (median, iqr)	10 (9)	11 (9)
ASPECTS > 7 (%, n/N)	77.4% (319/412)	78.0% (323/410)
OCSP clinical stroke type		
TACS	24.3% (101)	23.4% (97)
PACS	55.3% (230)	56.0% (232)
LACS	12.0% (50)	11.1% (46)
POCS	8.4% (35)	9.4% (39)
Thrombolysis	83.2% (246)	86.0% (356)
Intravenous tPA only	66.6% (277)	69.8% (289)
Intravenous tPA plus any endovascular procedure	16.6% (69)	16.2% (67)
Any endovascular procedure only	5.8% (24)	2.9% (12)
No thrombolysis	11.1% (46)	11.1% (46)
Systolic BP, mm Hg (mean, SD)	155 (28)	157 (30)
Glucose, mmol/L (mean, SD)	7.1 (2.5)	7.7 (3.7)
Hemoglobin, g/L (mean, SD)	139 (17)	140 (18)
Creatinine, μmol/L (mean, SD)	86.3 (23.1)	90.3 (26.9)
ECG at baseline shows normal sinus rhythm (%, n)	72.3% (297)	72.9% (296)
Process Measures		
Stroke onset to initiation of study drug infusion (min) [median, iqr]	200 (82)	198 (75)

	Albumin (N=416)	Saline Control (N=414)
Stroke onset to initiation of intravenous tPA (min) [median, iqr]	126 (71)	131 (68)
Initiation of IV tPA to initiation of study drug infusion (min) [median, iqr]	60 (31)	60 (32)
Post-treatment – Fluids and Cardiac Status		
Total IV fluids administered within 48 hours of randomization (ml) (mean (SD); [min, max])	3284 (1669); [416,15006]	3249 (1629); [432, 11235]
ECG at 24 hours shows normal sinus rhythm (%, n)	70.3% (275)	78.3% (313)

tPA = tissue plasminogen activator; OCSP = Oxfordshire Community Stroke Project stroke classification (TACS = total anterior circulation syndrome; PACS = partial anterior circulation syndrome; LACS = lacunar syndrome; POCS = posterior circulation syndrome); BP = blood pressure; IV = intravenous; ECG = electrocardiogram

[*] Hill MD, Martin RH, Palesch YY, Moy CS, Tamariz D, Ryckborst KJ, Jones EB, Weisman D, Pettigrew C, Ginsberg MD: Safety analysis of the ALIAS Part 2 Multicenter Trial (manuscript in preparation)

[†] Race and ethnic group were self-reported.

[‡] The National Institutes of Health Stroke Scale (NIHSS) is a 42-point scale that quantifies neurological deficits in 11 categories, with 0 indicating normal function without deficits, and higher scores indicating greater severities of deficit.

[§] The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) uses computed tomography to assess 10 regions of the brain; a score of 1 indicates a normal region and 0 indicates a region showing signs of ischemia. Total scores range from 10 (no evidence of early ischemia) to 0 (all 10 regions of the affected hemisphere show early ischemic changes).