Analysis of The International Stroke Trial Database

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Irene Kimura Park

Background of the IST Dataset

- Prospective, randomized controlled trial conducted between 1991-1996
- Goal: to establish whether early administration of aspirin, subcutaneous heparin, both, or neither influenced clinical course of acute ischaemic stroke
- 2 × 3 factorial design = 6 treatments

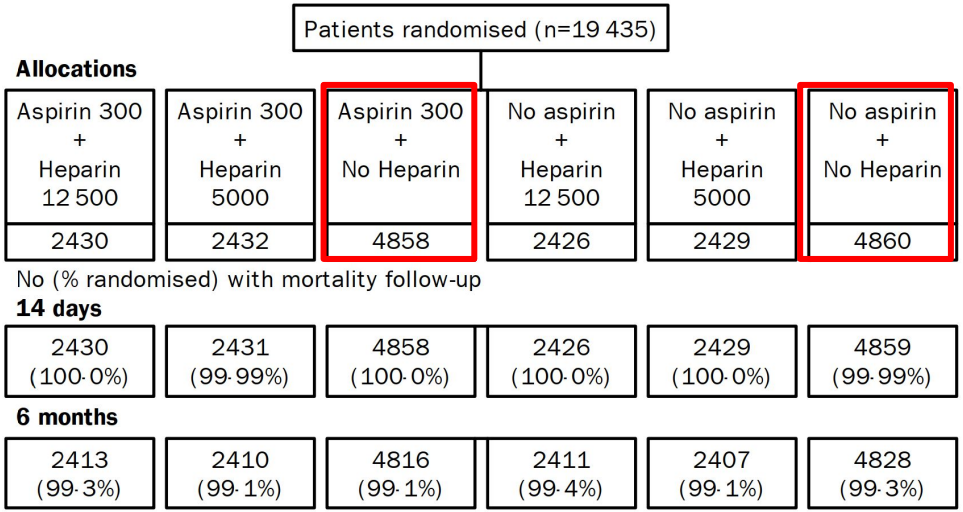
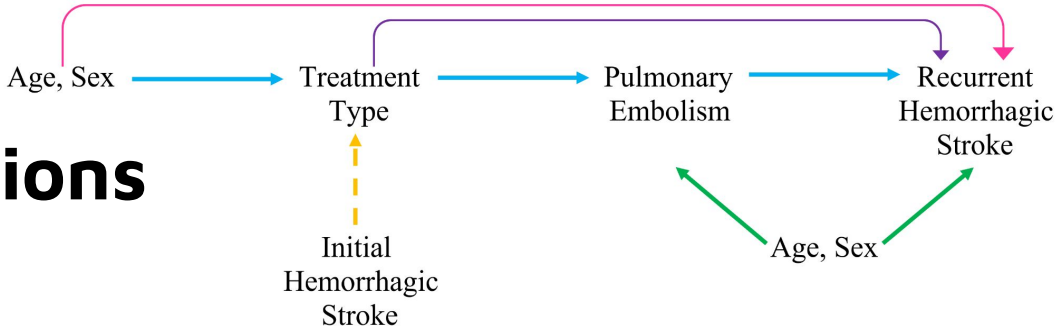


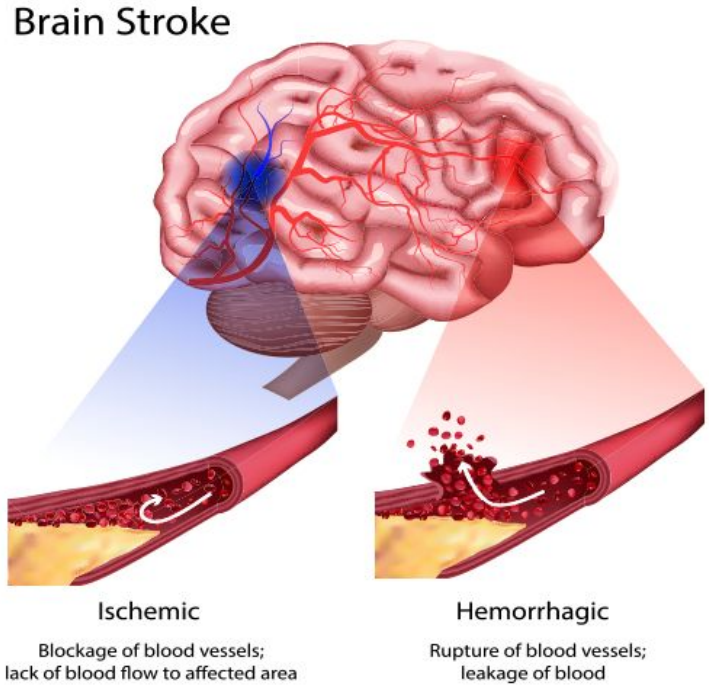
Figure 1: **Trial randomisation flow chart**



Research Questions

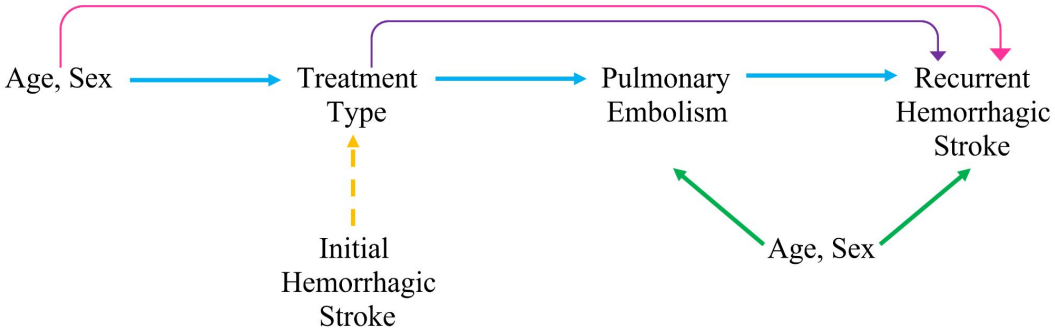
exposure = explanatory variable
outcome = response variable
confounder = variable that influences exposure and outcome
effect modifier = variable that changes the effect between exposure and outcome over its strata
mediator = variable that's an effect of the exposure and a cause of the outcome so it accounts for parts of total effect

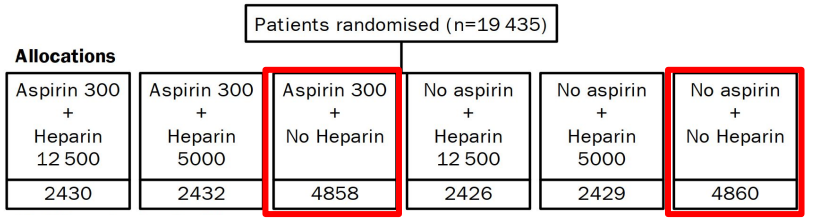
1. Does treatment type have an effect on the proportion of recurrent hemorrhagic stroke after 14 days of follow-up?
2. Does treatment type have an effect on the proportion of recurrent hemorrhagic stroke after 14 days of follow-up, adjusting for potential confounders age and sex?
3. Is there interaction between treatment type and initial hemorrhagic stroke on recurrent hemorrhagic stroke?
4. Does treatment type have an effect on the proportion of recurrent hemorrhagic stroke through pulmonary embolism, adjusting for potential confounders age and sex?



Statistical Methods

1. Subset dataset of interest
   a. Treatment Aspirin 300 mg & No Heparin 4,853 subjects
   b. Placebo No Aspirin & No Heparin 4,852 subjects
2. Logistic regression adjusting for confounders age and sex
3. Assess interaction between treatment and initial hemorrhagic stroke
4. Assess mediation through pulmonary embolism, adjusting for confounders age and sex





3 lost to follow-up
2 unknown

4 lost to follow-up
4 unknown

TOTAL
7 lost to follow-up
6 unknown
9,705 subjects

Baseline Demographics and Clinical Characteristics

Table 1.1		**Treatment** (aspirin 300 mg & no heparin) (n=4,858)	**Placebo** (no aspirin & no heparin) (n=4,860)	**Total** (n=9,718)
Sex (n,%)	Female	2,309 (47.53%)	2,250 (46.30%)	4,559 (46.91%)
	Male	2,549 (52.47%)	2,610 (53.70%)	5,159 (53.09%)
Age (mean, SD)		71.77 (11.63)	71.61 (11.72)	71.69 (11.68)
Conscious State (n,%)	Alert	3,681 (75.77%)	3,781 (77.80%)	7,462 (76.79%)
	Drowsy	1,109 (22.83%)	1,019 (20.97%)	2,128 (21.90%)
	Unconscious	68 (1.40%)	60 (1.23%)	128 (1.32%)
Visible Infarct (n,%)	Yes	1,611 (33.16%)	1,631 (33.56%)	3,242 (33.36%)
	No	3,247 (66.84%)	3,229 (66.44%)	6476 (66.64%)
SBP (mean, SD)		159.47 (27.52)	160.08 (27.90)	159.91 (27.71)

Baseline Demographics and Clinical Characteristics Cont.

Table 1.2		**Treatment** (aspirin 300 mg & no heparin) (n=4,858)	**Placebo** (no aspirin & no heparin) (n=4,860)	**Total** (n=9,718)
Face Deficit (n,%)	Yes	3,537 (72.81%)	3,517 (72.37%)	7,054 (72.59%)
	No	1,256 (25.85%)	1,269 (26.11%)	2,525 (25.98%)
	Can't Assess	65 (1.34%)	74 (1.52%)	139 (1.43%)
Arm/Hand Deficit (n,%)	Yes	4,155 (85.53%)	4,157 (85.53%)	8,312 (85.53%)
	No	675 (13.89%)	666 (13.70%)	1,341 (13.80%)
	Can't Assess	28 (0.58%)	37 (0.76%)	65 (0.67%)
Leg/Foot Deficit (n,%)	Yes	3,639 (74.91%)	3,665 (75.41%)	7,304 (75.16%)
	No	1,150 (23.67%)	1,133 (23.31%)	2,283 (23.49%)
	Can't Assess	69 (1.42%)	62 (1.28%)	131 (1.35%)

Baseline Demographics and Clinical Characteristics Cont.

Table 1.2		**Treatment** (aspirin 300 mg & no heparin) (n=4,858)	**Placebo** (no aspirin & no heparin) (n=4,860)	**Total** (n=9,718)
Dysphagia (n,%)	Yes	2,156 (44.38%)	2,124 (43.70%)	4,280 (44.04%)
	No	2,561 (52.72%)	2,577 (53.02%)	5,138 (52.87%)
	Can't Assess	141 (2.90%)	159 (3.27%)	300 (3.09%)
Hemianopia(n,%)	Yes	792 (16.30%)	747 (15.37%)	1,539 (15.84%)
	No	3,048 (62.74%)	3,120 (64.20%)	6,168 (63.47%)
	Can't Assess	1,018 (20.96%)	993 (20.43%)	2,011 (20.69%)
Visuospatial Disorder (n,%)	Yes	836 (17.21%)	764 (15.72%)	1,600 (16.46%)
	No	3,161 (65.07%)	3,214 (66.13%)	6,375 (65.60%)
	Can't Assess	861 (17.72%)	882 (18.15%)	1,743 (17.94%)
Brainstem/Cerebellar Signs (n,%)	Yes	506 (10.42%)	546 (11.23%)	1,052 (10.83%)
	No	3,944 (81.19%)	3,936 (80.99%)	7,880 (81.09%)
	Can't Assess	408 (8.40%)	378 (7.78%)	786 (8.09%)

Crude and Adjusted Analysis Results

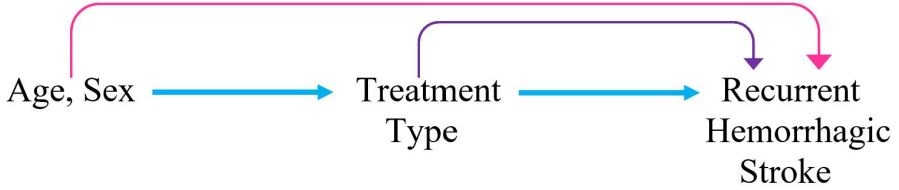


Table 2.1 - Crude logistic regression results

Effect	Parameter Estimate	Odds Ratio	95% Odds Ratio Confidence Limits	p-value
Treatment	0.4364	1.5471	0.724, 3.306	0.2601

Table 2.2 - Adjusted logistic regression results

Effect	Parameter Estimate	Odds Ratio	95% Odds Ratio Confidence Limits	p-value
Treatment	0.4436	1.5583	0.729, 3.331	0.2525
Sex	0.1809	1.1983	0.544, 2.590	0.6455
Age	-0.0282	0.9722	0.945, 1.001	0.0549

Effect Modification/ Interaction Analysis

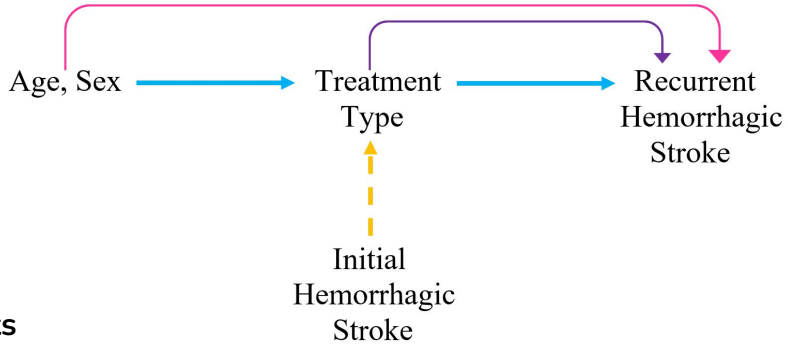


Table 3 - Adjusted logistic regression with interaction results

Effect	Parameter Estimate	Odds Ratio	95% Odds Ratio Confidence Limits	p-value
Treatment	0.3290	-	-	0.4795
Initial Hemorrhagic Stroke	2.5992	-	-	0.0001
Trt * initial_hemstroke	0.3600	-	-	0.6742
Aspirin vs Placebo, **NO** initial_hemstroke	-	1.390	0.558, 3.459	-
Aspirin vs Placebo, **YES** initial_hemstroke	-	1.992	0.487, 8.150	-
Sex	0.1706	1.186	0.546, 2.578	0.6666
Age	-0.0322	0.968	0.940, 0.998	0.0342

Mediation Analysis

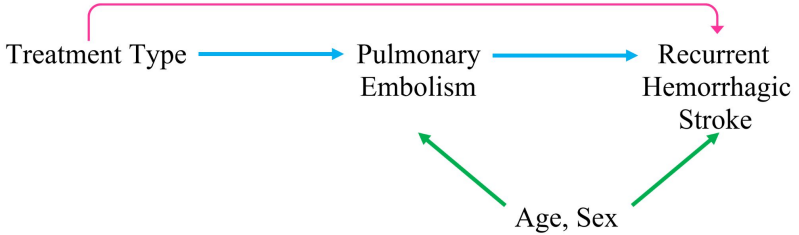
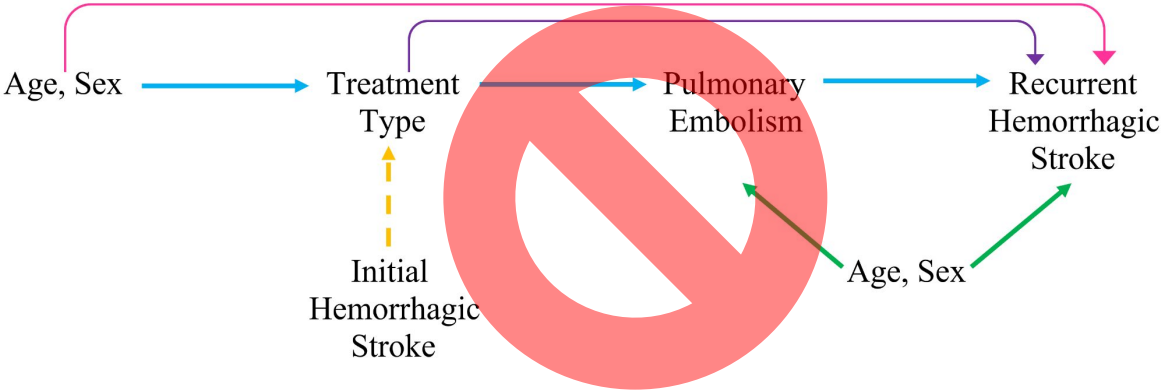


Table 4 - Causal mediation analysis results

	Parameter Estimate	95% CI Lower	95% CI Upper	p-value
Natural Direct Effect	0.0013633	-0.0007973	0.00	0.23
Natural Indirect Effect	-0.0000781	-0.0004260	0.00	0.25
Total Effect	0.0013131	-0.0009073	0.00	0.25
Proportion Mediated	-0.0211428	-0.6576451	0.23	0.45

Indirect effect and total effect have different signs!
Cannot interpret proportion mediated

Conclusions



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Questions?