

THE LANCET **Neurology**

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Whiteley WN, Adams HP Jr, Bath PMW, et al. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol* 2013; published online May 2. [http://dx.doi.org/10.1016/S1474-4422\(13\)70079-6](http://dx.doi.org/10.1016/S1474-4422(13)70079-6).

Targeted use of heparin, heparinoids, or low-molecularweight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials

SUPPLEMENTAL MATERIAL

Guideline organisation and date	Title	For the prevention of recurrent stroke		For the prevention of venous thromboembolism			
		Uncertain benefit of targeting	Avoid all	Treat all	Avoid all	Treat at 'high risk' of VTE	Avoid if 'high risk' of haemorrhage
Acute stroke guidelines							
Institute for Clinical Systems Improvement 2010	Diagnosis and treatment of ischemic stroke	✓	✓	✓			
Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association 2002	Anticoagulants and antiplatelet agents in acute ischemic stroke		✓			✓	✓
American College of Chest Physicians 2012	Antithrombotic and thrombolytic therapy for ischemic stroke		✓	✓			
National Institute for Health and Clinical Excellence 2008	Diagnosis and Initial management of acute stroke and transient ischaemic attack		✓			✓	
American Association of Neuroscience Nurses 2008	Guide to the care of the hospitalized patient with ischemic stroke					✓	✓
Canadian best practice recommendations for stroke care 2010	Acute stroke management		✓			✓	✓
Scottish Intercollegiate Guidelines Network 2008	Management of patients with stroke or TIA: assessment, investigation, immediate		✓			✓	

Guideline organisation and date	Title	For the prevention of recurrent stroke		For the prevention of venous thromboembolism			
		Uncertain benefit of targeting	Avoid all	Treat all	Avoid all	Treat at 'high risk' of VTE	Avoid if 'high risk' of haemorrhage
	management and secondary prevention						
Singapore Ministry of Health 2009	Stroke and transient ischaemic attacks. Assessment, investigation, immediate management and secondary prevention		✓		✓		
European Stroke Organisation 2008	Guidelines for the management of Ischaemic Stroke		✓			✓	
American Heart Association/ American Stroke Association Stroke Council, 2007	Guidelines for the Early Management of Adults With Ischemic Stroke		✓				
National Stroke Foundation, Australia 2010	Clinical Guideline for Stroke Management					✓	
Prevention of VTE guidelines							
Institute for Clinical Systems Improvement 2011	Venous thromboembolism prophylaxis			✓			
American College of Physicians 2011	Venous thromboembolism prophylaxis in hospitalized patients					✓	✓
National Institute for Health and Clinical Excellence 2010	Venous thromboembolism: reducing the risk					✓	✓
Scottish Intercollegiate Guidelines Network 2010	Prevention and management of venous thromboembolism					✓	
Finnish Medical Society Duodecim 2008	Prevention of venous thromboembolism.			✓			

Supplementary table 1 Baseline characteristics of patients

	IST		TOAST		FISS-tris		HAEST		TAIST		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
	N=18836		N=1281		N=603		N=449		N=1486		N=22655	
Age (years)												
<50	1042	5.5%	137	10.7%	53	8.8%	1	0.2%	73	4.9%	1306	5.8%
50-59	1759	9.3%	231	18.0%	95	15.8%	8	1.8%	136	9.2%	2229	9.8%
60-69	4254	22.6%	384	30.0%	182	30.2%	45	10.0%	330	22.2%	5195	22.9%
70-79	6472	34.4%	420	32.8%	217	36.0%	167	37.2%	561	37.8%	7837	34.6%
>=80	5309	28.2%	109	8.5%	56	9.3%	228	50.8%	386	26.0%	6088	26.9%
Sex												
Women	8741	46.4%	504	39.3%	245	40.6%	248	55.2%	678	45.6%	10416	46.0%
Men	10095	53.6%	777	60.7%	358	59.4%	201	44.8%	808	54.4%	12239	54.0%
Time from stroke onset to randomisation (hrs)												
0-6	2996	15.9%	48	3.7%	9	1.5%	24	5.3%	53	3.6%	3130	13.8%
6-12	3986	21.2%	350	27.3%	38	6.3%	101	22.5%	219	14.7%	4694	20.7%
12-24	5408	28.7%	862	67.3%	205	34.0%	180	40.1%	428	28.8%	7083	31.3%
>24h	6446	34.2%	6	0.5%	350	58.0%	143	31.8%	761	51.2%	7706	34.0%
missing	0	0.0%	15	1.2%	1	0.2%	1	0.2%	25	1.7%	42	0.2%
History of MI												
no	-	-	928	72.4%	549	91.0%	292	65.0%	1229	82.7%	2998	13.2%
yes	-	-	343	26.8%	50	8.3%	157	35.0%	232	15.6%	782	3.5%
missing	-	-	10	0.8%	4	0.7%	0	0.0%	25	1.7%	18875	83.3%
History of stroke												
no	-	-	1038	81.0%	500	82.9%	341	75.9%	1271	85.5%	3150	13.9%
yes	-	-	232	18.1%	103	17.1%	108	24.1%	194	13.1%	637	2.8%
missing	-	-	11	0.9%	0	0.0%	0	0.0%	21	1.4%	18868	83.3%

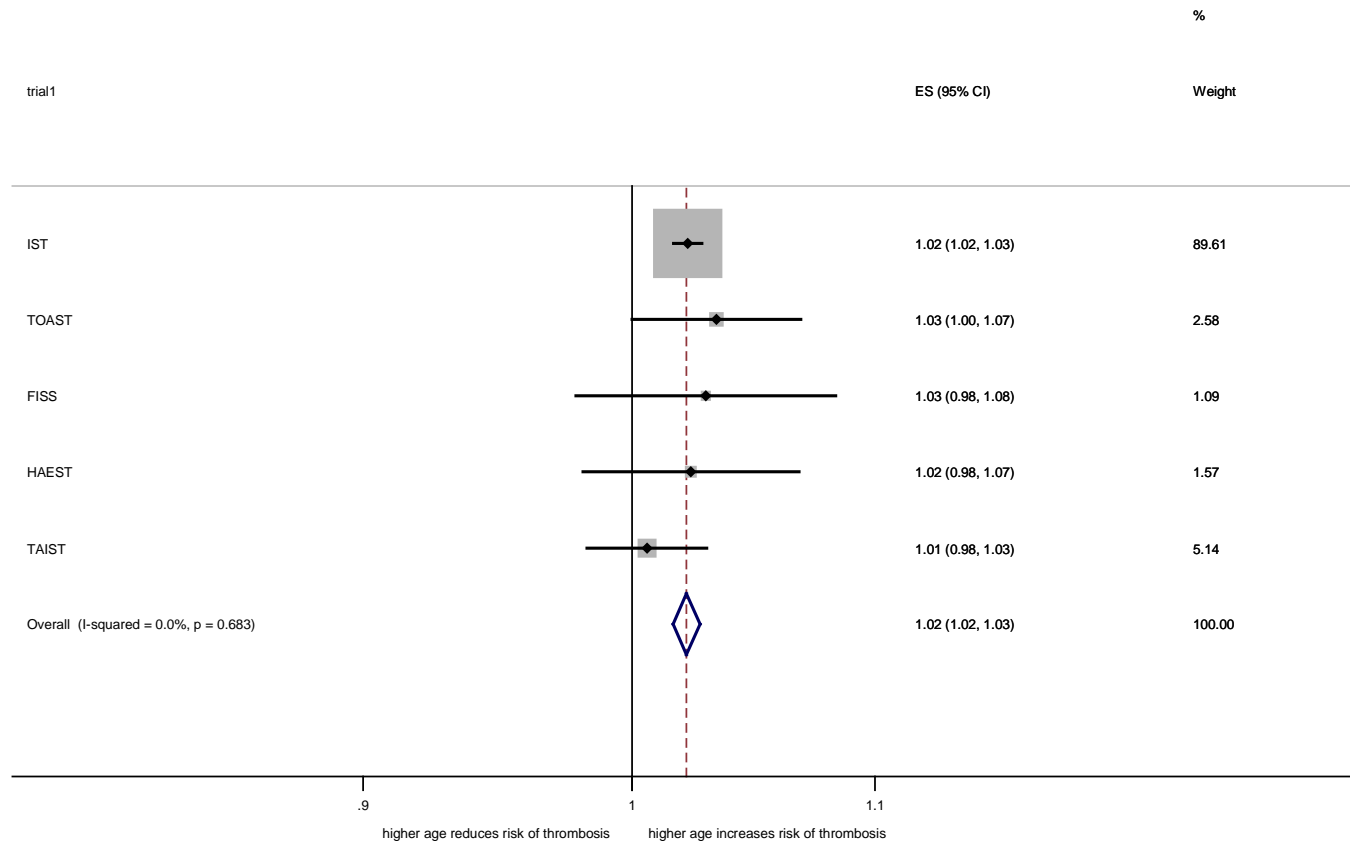
	IST		TOAST		FISS-tris		HAEST		TAIST		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
History of hypertension												
no	-	-	413	32.2%	169	28.0%	270	60.1%	726	48.9%	1578	7.0%
yes	-	-	850	66.4%	434	72.0%	179	39.9%	728	49.0%	2191	9.7%
missing	-	-	18	1.4%	0	0.0%	0	0.0%	32	2.2%	18886	83.4%
History of diabetes												
no	-	-	893	69.7%	356	59.0%	383	85.3%	0	0.0%	1632	7.2%
yes	-	-	374	29.2%	247	41.0%	66	14.7%	0	0.0%	687	3.0%
missing	-	-	14	1.1%	0	0.0%	0	0.0%	1486	100.0%	20336	89.8%
Antiplatelet drug prior to randomisation												
no	15007	79.7%	732	57.1%	402	66.7%	248	55.2%	922	62.0%	17311	76.4%
yes	3829	20.3%	528	41.2%	193	32.0%	201	44.8%	563	37.9%	5314	23.5%
missing	0	0.0%	21	1.6%	8	1.3%	0	0.0%	1	0.1%	30	0.1%
OCSP stroke classification												
TACS	4452	23.6%	439	34.3%	34	5.6%	102	22.7%	523	35.2%	5550	24.5%
PACS	7627	40.5%	148	11.6%	169	28.0%	238	53.0%	473	31.8%	8655	38.2%
LACS	4524	24.0%	540	42.2%	279	46.3%	71	15.8%	422	28.4%	5836	25.8%
POCS	2177	11.6%	153	11.9%	121	20.1%	36	8.0%	66	4.4%	2553	11.3%
missing	56	0.3%	1	0.1%	0	0.0%	2	0.4%	2	0.1%	61	0.3%
NIH Stroke Scale¹												
0-5	1309	6.9%	449	35.1%	294	48.8%	109	24.3%	153	10.3%	2314	10.2%
6-10	3893	20.7%	463	36.1%	214	35.5%	135	30.1%	481	32.4%	5186	22.9%
11-15	8680	46.1%	207	16.2%	68	11.3%	78	17.4%	455	30.6%	9488	41.9%
16-20	2389	12.7%	75	5.9%	18	3.0%	73	16.3%	226	15.2%	2781	12.3%
>20	1654	8.8%	87	6.8%	5	0.8%	54	12.0%	171	11.5%	1971	8.7%

¹ Converted from Scandinavian stroke (TAIST, HAEST) or markers of stroke severity (IST)

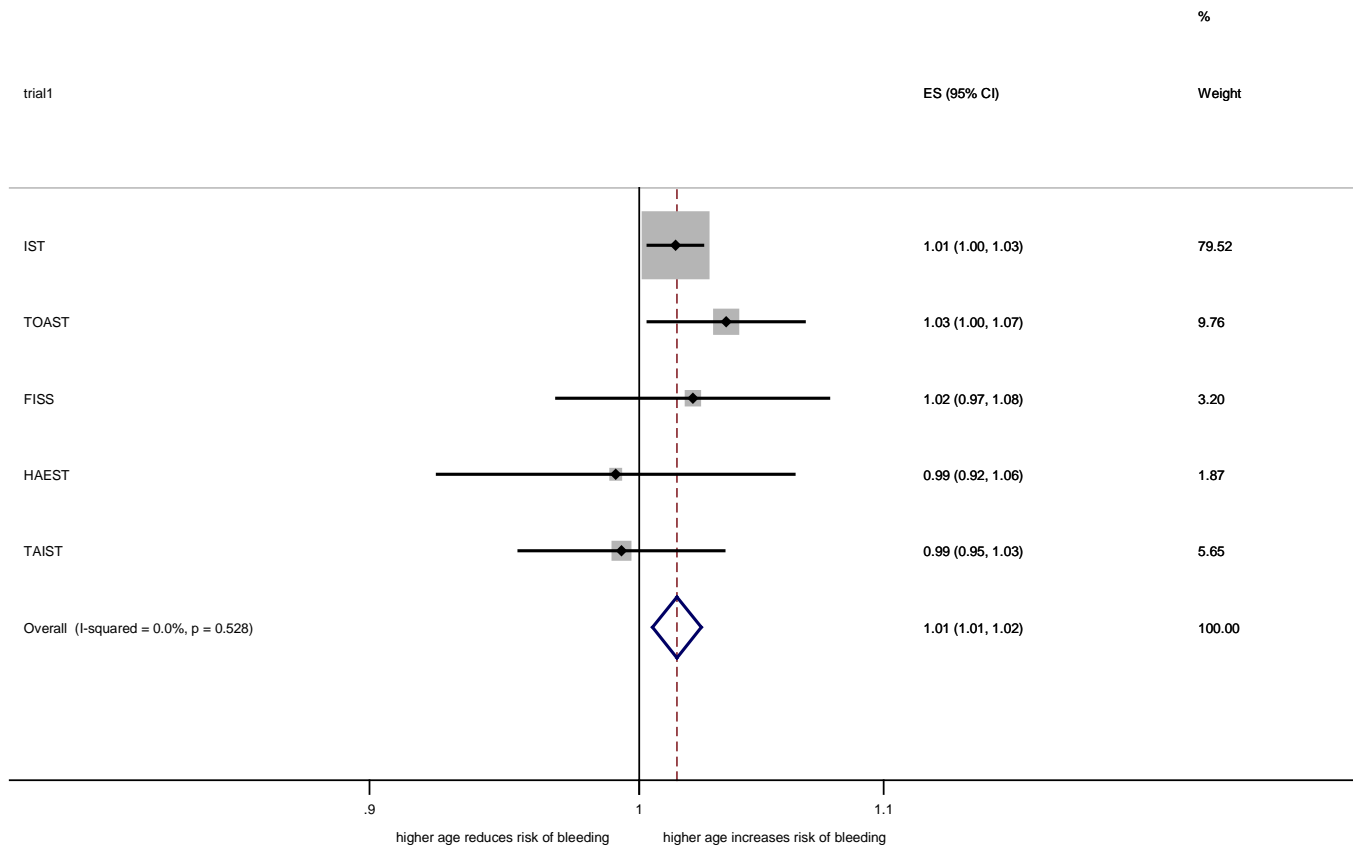
	IST		TOAST		FISS-tris		HAEST		TAIST		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Systolic blood pressure (mmHg)												
<145	6031	32.0%	434	33.9%	227	37.6%	106	23.6%	477	32.1%	7275	32.1%
146-170	7341	39.0%	594	46.4%	239	39.6%	172	38.3%	608	40.9%	8954	39.5%
>170	5464	29.0%	253	19.8%	133	22.1%	171	38.1%	395	26.6%	6416	28.3%
Atrial fibrillation												
no	14792	78.5%	1166	91.0%	603	100.0%	31	6.9%	1305	87.8%	17897	79.0%
yes	3090	16.4%	115	9.0%	0	0.0%	418	93.1%	181	12.2%	3804	16.8%
missing	954 ²	5.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	954	4.2%
Evidence of infarction baseline CT												
no	12449	66.1%	952	74.3%	160	26.5%	103	22.9%	587	39.5%	14251	62.9%
yes	6387	33.9%	329	25.7%	354	58.7%	346	77.1%	898	60.4%	8314	36.7%
missing	0	0.0%	0	0.0%	89	14.8%	0	0.0%	1	0.1%	90	0.4%

Abbreviations. OCSP=Oxfordshire community stroke project; TACS=total anterior circulation syndrome; PACS=partial anterior circulation stroke syndrome; LACS=lacunar stroke syndrome; POCS=posterior circulation stroke syndrome.

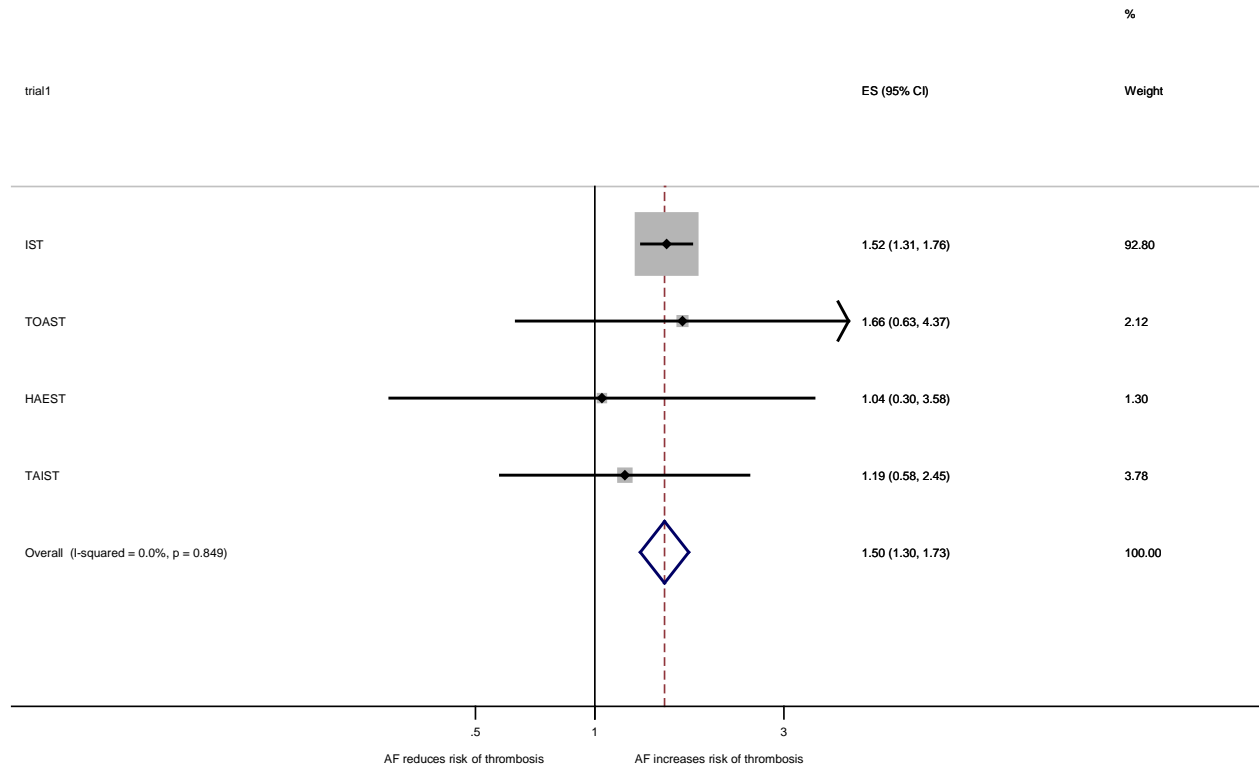
² Atrial fibrillation not recorded in the pilot phase of the trial (n=954).



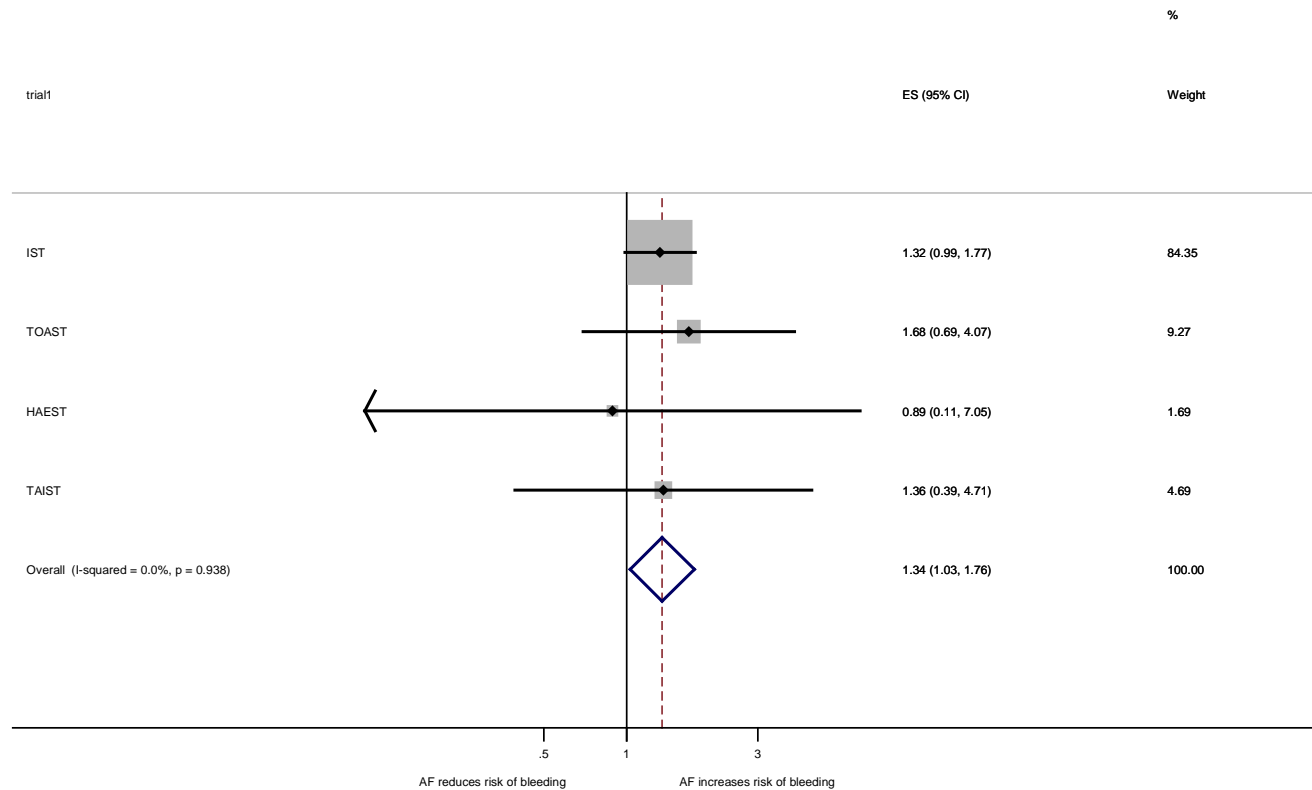
Supplementary Figure 1. The odds ratio (ES) for the association between a one year increase in age with thrombotic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.



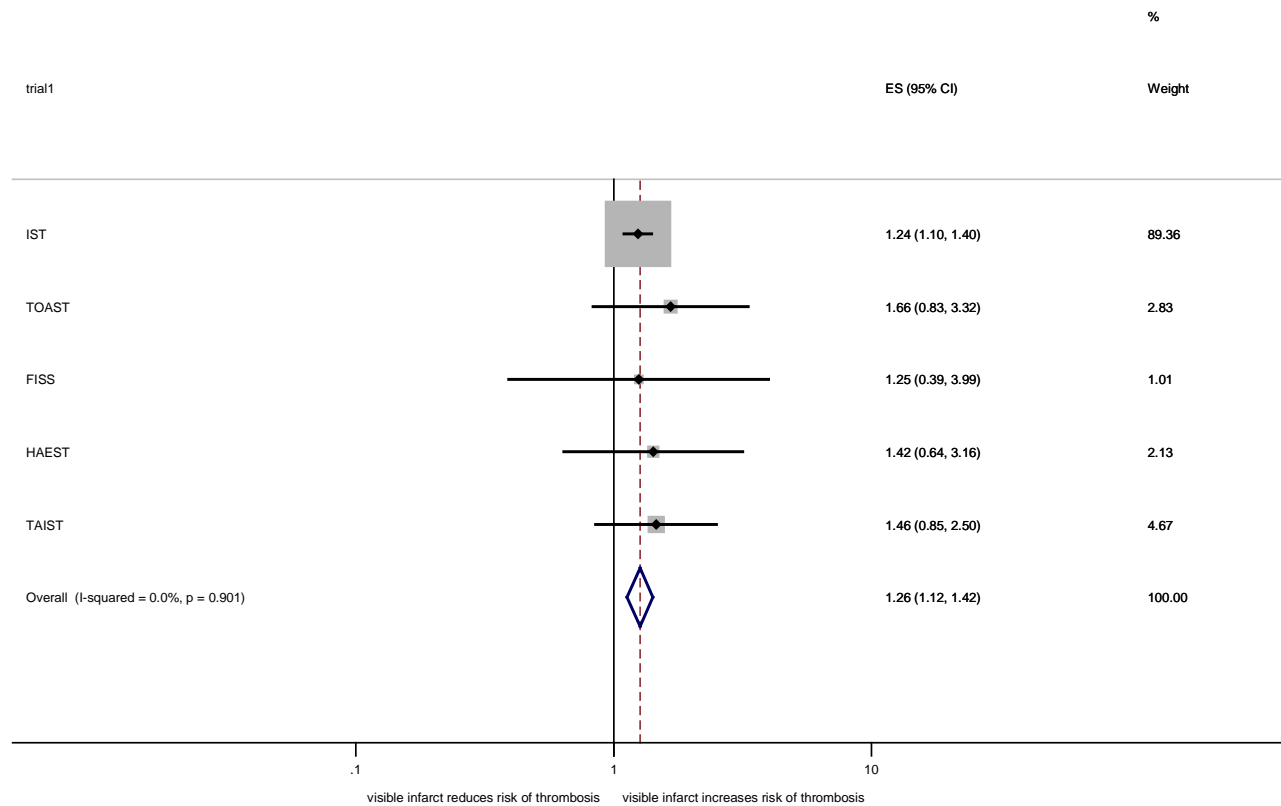
Supplementary Figure 2. The odds ratio (ES) between a one year increase in age with haemorrhagic events 2 weeks post ischaemic stroke IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.



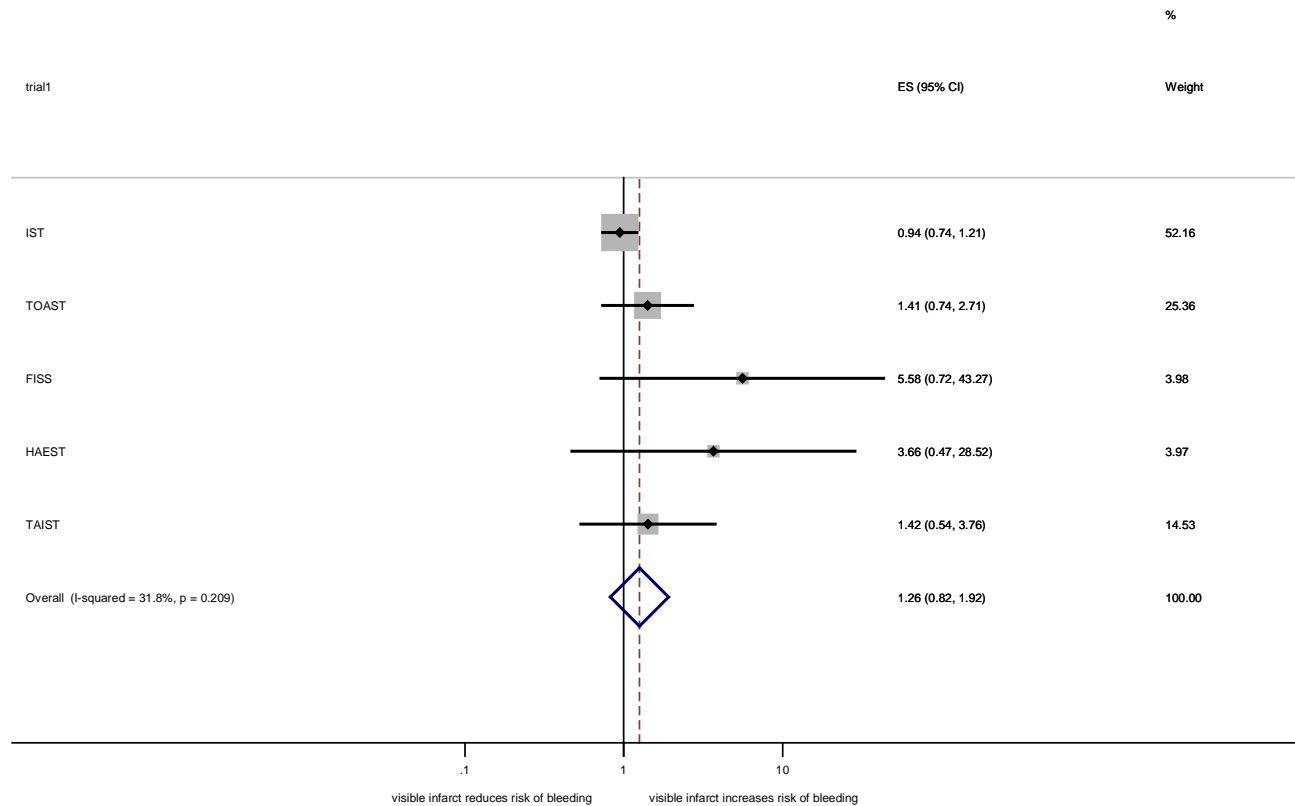
Supplementary Figure 3. The odds ratio (ES) between the presence of AF with thrombotic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity. AF defined uniformly across trials.



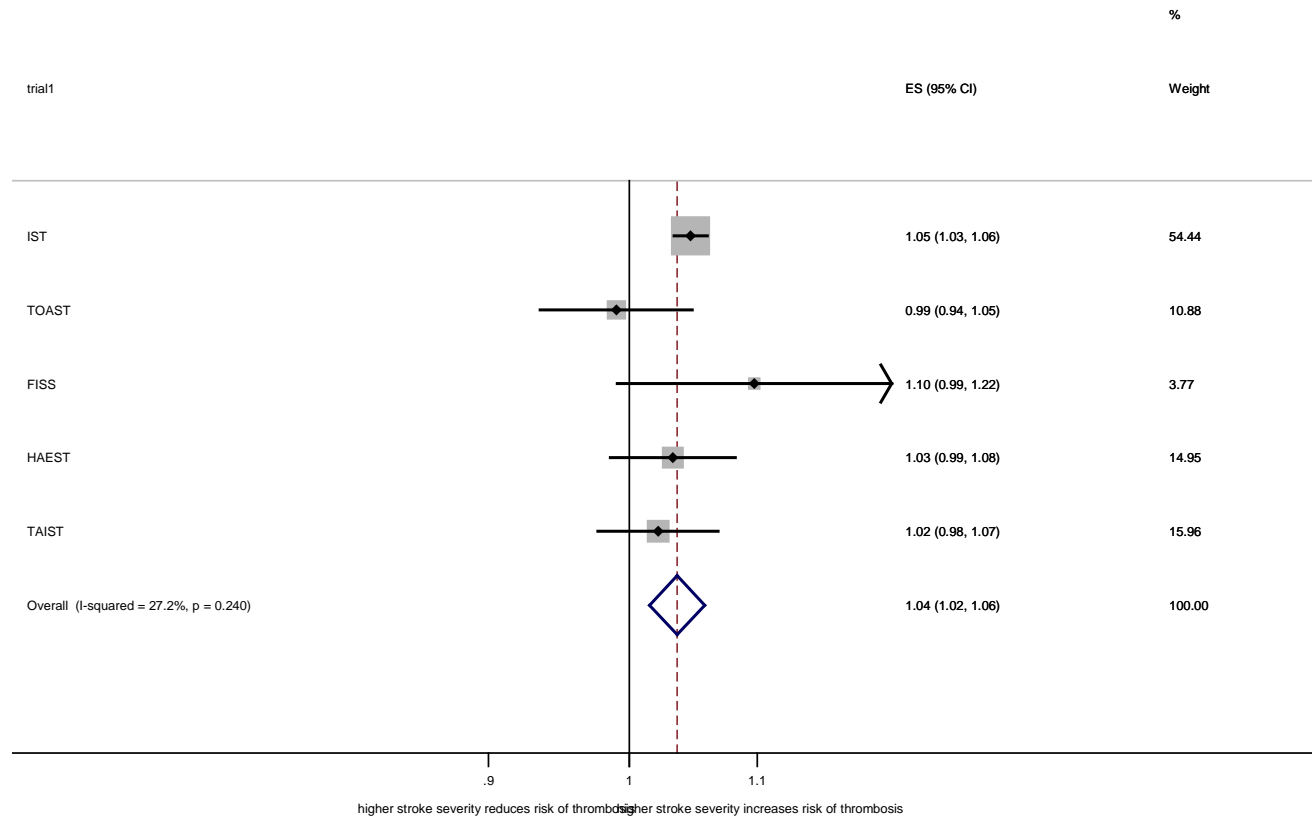
Supplementary Figure 4. The odds ratio (ES) between the presence of AF with haemorrhagic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity. AF defined uniformly across trials.



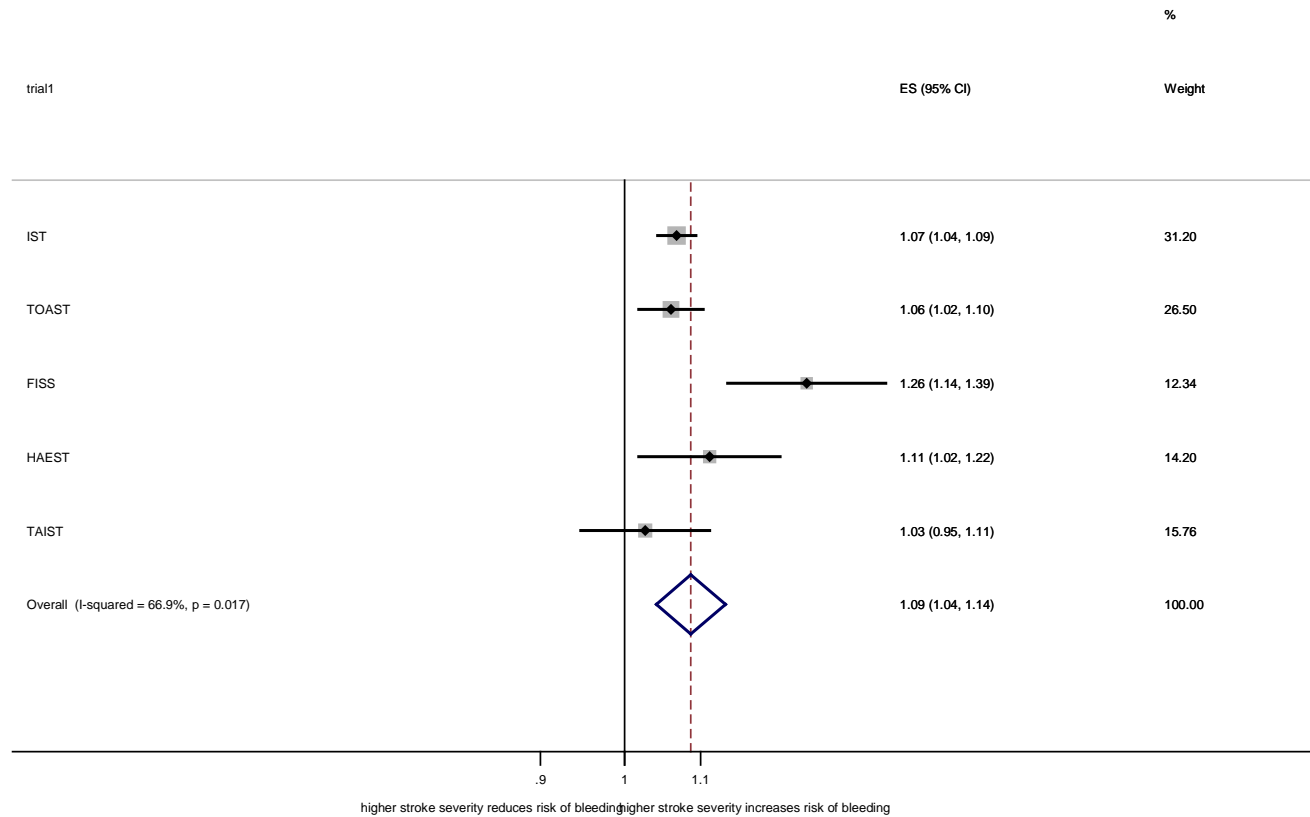
Supplementary Figure 5. The odds ratio (ES) between the presence of CT visible infarct with thrombotic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.



Supplementary Figure 6. The odds ratio (ES) between the presence of CT visible infarct with haemorrhagic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.



Supplementary figure 7. The odds ratio (ES) between a one year increase in NIHSS with thrombotic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.



Supplementary figure 8. The odds ratio (ES) between a one year increase in NIHSS with haemorrhagic events 2 weeks post ischaemic stroke. IST: International Stroke Trial; TOAST: Trial of ORG 10172 in Acute Stroke Treatment; TAIST: Tinzaparin in Acute Ischaemic Stroke Trial; HAEST: Heparin in Acute Embolic Stroke Trial; FISS-tris: Fraxiparin in Stroke Study for the treatment of ischemic stroke. I squared: a measure of statistical heterogeneity.