SUPPLEMENTAL MATERIAL

Optimal Duration of Aspirin plus Clopidogrel After Ischemic Stroke or TIA: A Systematic Review and Meta-Analysis

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Contents

Studies	Randomization	Allocation concealment	Blinding	Deviation from intended intervention	Outcome assessment bias	Free of other biases
POINT 2018[1]						
COMPRESS 2016[2]						
He et al 2014[3]						
Yi et al 2014[4]						
CHANCE 2013[5]						
SPS 3 2012[6]						
CLAIR 2010[7]						
FASTER 2007[8]						
CHARISMA 2006[9]						
CARESS 2005[10]						
Low risk=Green; Unclear risk=White; High risk= Red						

Study	Major bleeding criteria
POINT 2018[1]	Symptomatic intracranial hemorrhage, intraocular bleeding causing vision loss, transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage
COMPRESS 2016[2]	Intraocular hemorrhage, significant disability by bleeding, or requiring the transfusion of ≤3 units of blood
He et al 2014[3]	Not mentioned
Yi et al 2014[4]	Any symptomatic intracranial hemorrhage or any hemorrhage requiring blood transfusion or prolonged hospitalization was considered as serious hemorrhage
CHANCE 2013[5]	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition
SPS 3 2012[6]	Requiring transfusion of red cells or surgery or resulting in permanent functional sequelae or death
CLAIR 2010[7]	Any symptomatic intracranial hemorrhage or any hemorrhage requiring blood transfusion or prolonged stay in hospital.
FASTER 2007[8]	Life threatening, resulting in hemodynamic compromise or hypovolemic shock, requiring inotropic support or other means to maintain cardiac output, requiring blood transfusion of more than 2 units of packed red blood cells, or associated with a fall in hemoglobin greater than or equal to 5 g/L
CHARISMA 2006[9]	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definition
CARESS 2005[10]	Not mentioned

Endpoints	**Studies *(n*)**	**RD (95 % CI)**	**p-value**
Short-term outcomes			
Recurrent Ischemic Stroke	6	-0.035 (-0.047, -0.023)	<0.001
Major bleeding	7	0.001 (-0.001, 0.002)	0.42
Major adverse cardiovascular events	5	-0.026 (-0.037, -0.015)	<0.001
All-cause mortality	4	-0.000 (-0.003, 0.004)	0.82
Mid-term outcomes			
Recurrent Ischemic Stroke	2	-0.018 (-0.031, -0.006)	0.004
Major bleeding	2	0.012 (-0.006, 0.030)	0.21
Major adverse cardiovascular events	2	-0.016 (-0.029, -0.004)	0.01
All-cause mortality	2	0.003 (-0.001, 0.007)	0.20
Long-term outcomes			
Recurrent Ischemic Stroke	2	-0.006 (-0.033, 0.022)	0.69
Major bleeding	2	0.024 (0.003, 0.044)	0.02
Major adverse cardiovascular events	1	-0.015 (-0.037, 0.007)	0.19
All-cause mortality	1	0.023 (0.006, 0.041)	0.01

Studies	Arms	n	Age (years)	Male (%)	Presentation		HTN (%)	IHD (%)	DM (%)	Smoking (%)	Prior Stroke (%)	Prior Aspirin use (%)	Prior Clopidogrel use (%)
					TIA (%)	Stroke (%)							
POINT 2018[1]	A+C	2432	65.0	54.9	43.4	56.6	69.9	10.6	28.0	20.4	-	58.3	2.0
	A	2449	65.0	55.2	43.0	57.0	68.9	9.8	27.1	20.8	-	57.0	1.7
COMPRESS 2016[2]	A+C	174	68.0	65.5	0.0	100	64.4	4.6	33.3	40.8	11.5	-	-
	A	175	67.0	61.7	0.0	100	68.0	4.6	31.4	36.0	9.1	-	-
He et al 2014[3]	A+C	321	62.9	57	6.8	93.2	66.4	27.4	43.0	50.2	32.4	-	-
	A	326	61.5	56.7	4.9	95.1	68.7	28.2	39.3	50.6	35.9	-	-
Yi et al 2014[4]	A+C	284	69.2	54.9	-	100	71.8	1.4	37.0	39.4	-	0.0	0.0
	A	286	70.1	54.9	-	100	73.4	1.0	38.5	40.6	-	0.0	0.0
CHANCE 2013[5]	A+C	2584	63.0	67.0	27.7	72.3	66.4	1.7	21.3	43.2	20.0	21.4	0.5
	A	2586	62.0	65.3	28.2	71.8	65.1	2.0	21.0	42.7	20.0	22.1	0.5
SPS 3 2012[6]	A+C	1517	63.0	62.0	3.0	97.0	76.0	10.0	35.0	20.0	15.0	28.0	-
	A	1503	63.0	64.0	3.0	97.0	74.0	11.0	38.0	21.0	15.0	28.0	-
CLAIR 2010[7]	A+C	46	59.2	78.0	-	-	60.0	7.0	46.0	46.0	-	-	-
	A	52	56.4	77.0	-	-	69.0	6.0	31.0	58.0	-	-	-
FASTER 2007[8]	A+C	198	68.0	57.6	-	-	46.5	5.6	12.1	27.3	6.1	-	-
	A	194	68.2	48.4	-	-	54.6	4.1	9.3	24.7	8.8	-	-
CHARISMA 2006[9]	A+C	7802†	64.0	70.3	-	-	73.3	34.2	42.3	20.1	24.9	-	-
	A	7801†	64.0	70.2	-	-	73.9	34.9	41.7	20.3	24.3	-	-
CARESS 2005[10]	A+C	51	66.4	68.6	37.3	62.7	74.5	11.8	31.4	-	5.9	90.2	-
	A	56	62.8	69.6	42.6	57.4	55.4	17.9	32.1	-	7.1	92.9	-

† Total trial population

Abbreviations: A, aspirin; C, clopidogrel; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; n, number of patients; TIA, transient ischemic attack.

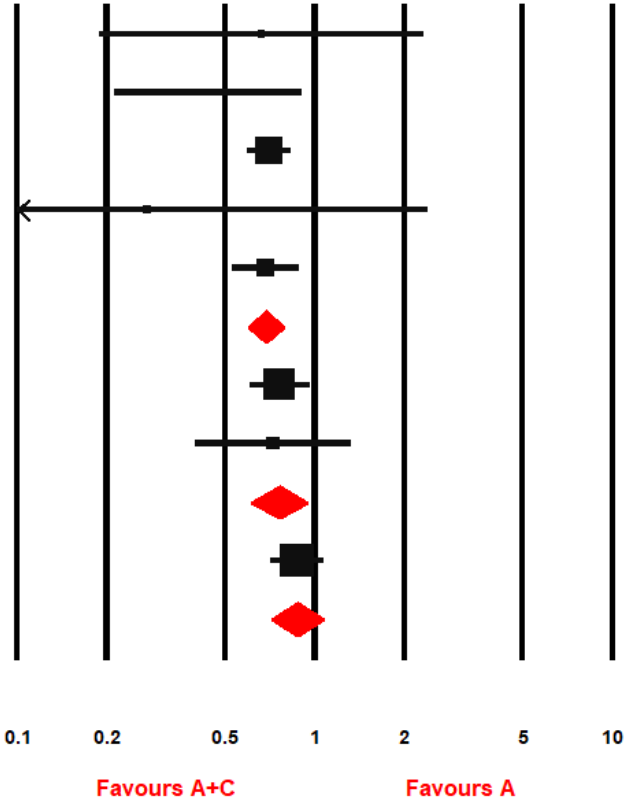
Variables	Slope (95 % Confidence Interval)	P-value
Recurrent Ischemic Stroke		
Year	0.001 (-0.043, 0.045)	0.97
Age (years)	-0.037 (-0.118, 0.045)	0.37
Male (%)	0.003 (-0.020, 0.027)	0.79
Hypertension (%)	0.010 (-0.014, 0.034)	0.41
Diabetes Mellitus	0.001 (-0.014, 0.017)	0.88
Ischemic Heart Disease (%)	0.002 (-0.019, 0.024)	0.84
Current Smoking (%)	-0.006 (-0.016, 0.004)	0.26
Major Bleeding		
Year	0.013 (-0.091, 0.117)	0.80
Age (years)	-0.069 (-0.289, 0.151)	0.54
Male (%)	0.036 (-0.037, 0.108)	0.33
Hypertension (%)	0.030 (-0.040, 0.099)	0.40
Diabetes Mellitus	0.001 (-0.066, 0.068)	0.98
Ischemic Heart Disease (%)	-0.001 (-0.032, 0.029)	0.93
Current Smoking (%)	-0.006 (-0.027, 0.015)	0.57

Ongoing trials
The **THALES** (Acute STroke or Transient IscHemic Attack Treated with TicAgrelor and ASA for PrEvention of Stroke and Dealth; ClinicalTrials.gov Identifier: NCT03354429) comparing ticagrelor and aspirin combination with aspirin alone in patients with acute IS or TIA to evaluate the composite of stroke and death at 30 days.
The **CSPS.com** trial (Cilostazol Stroke Prevention Study for Antiplatelet Combination; ClinicalTrials.gov Identifier: NCT01995370) comparing the efficacy and safety of aspirin and cilostazol with aspirin or clopidogrel monotherapy in high risk stroke patients.
The **ATAMIS** (Antiplatelet Therapy in Acute Mild-Moderate Ischemic Stroke) (ClinicalTrials.gov Identifier: NCT02869009) comparing efficacy and safety of dual-antiplatelet therapy versus aspirin monotherapy in patients with acute mild-moderate ischemic stroke ($4 \leq NIHSS \leq 10$)

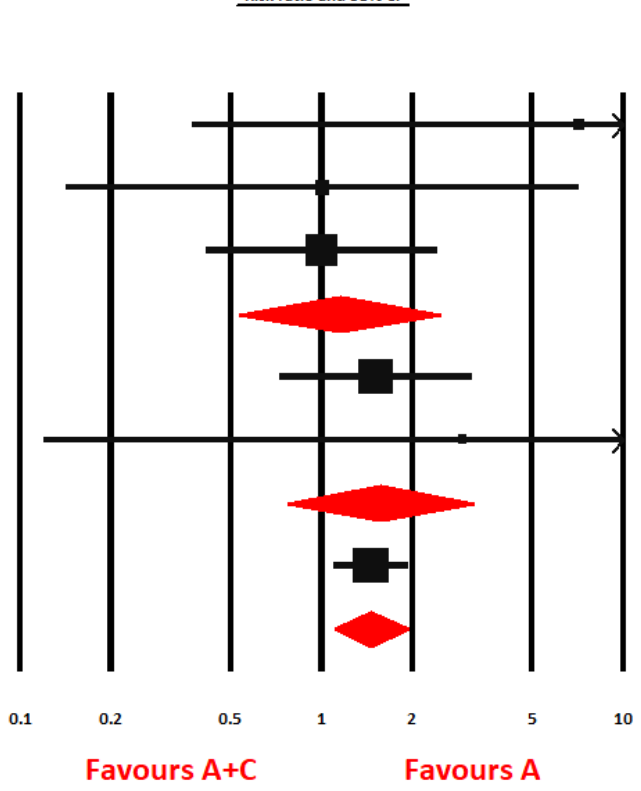
Search Strategy:

(("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) OR ("cerebral infarction"[MeSH Terms] OR ("cerebral"[All Fields] AND "infarction"[All Fields]) OR "cerebral infarction"[All Fields]) OR ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields] OR ("cerebrovascular"[All Fields] AND "disease"[All Fields]) OR "cerebrovascular disease"[All Fields]) OR ("transient ischaemic attacks"[All Fields] OR "ischemic attack, transient"[MeSH Terms] OR ("ischemic"[All Fields] AND "attack"[All Fields] AND "transient"[All Fields]) OR "transient ischemic attack"[All Fields] OR ("transient"[All Fields] AND "ischemic"[All Fields] AND "attacks"[All Fields]) OR "transient ischemic attacks"[All Fields]) OR ("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) OR ("clopidogrel"[Supplementary Concept] OR "clopidogrel"[All Fields]) OR (("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) AND ("clopidogrel"[Supplementary Concept] OR "clopidogrel"[All Fields]) AND combination[All Fields]) OR antiplatelets[All Fields] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomized controlled trials"[All Fields])

Outcome	Comparison	Study name	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
MACE	Short-term	COMPRESS 2016	0.66	0.19	2.31	-0.65	0.52
		Yi et al 2014	0.44	0.21	0.90	-2.24	0.03
		CHANCE 2013	0.70	0.60	0.83	-4.16	0.00
		CARESS 2005	0.27	0.03	2.38	-1.17	0.24
		POINT 2018 (0-30)	0.69	0.53	0.88	-2.92	0.00
			0.68	0.60	0.78	-5.51	0.00
	Mid-term	POINT 2018	0.76	0.61	0.96	-2.33	0.02
		FASTER 2007	0.72	0.40	1.31	-1.06	0.29
			0.76	0.61	0.94	-2.55	0.01
	Long-term	SPS 3 2012	0.87	0.71	1.07	-1.32	0.19
			0.87	0.71	1.07	-1.32	0.19



Outcome	Comparison	Study name	Statistics for each study				
			Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
All-cause mortality	Short-term	COMPRESS 2016	7.16	0.37	137.60	1.31	0.19
		Yi et al 2014	1.01	0.14	7.10	0.01	0.99
		CHANCE 2013	1.00	0.42	2.40	0.00	1.00
			1.15	0.53	2.48	0.34	0.73
	Mid-term	POINT 2018	1.51	0.73	3.13	1.11	0.27
		FASTER 2007	2.94	0.12	71.72	0.66	0.51
			1.56	0.77	3.18	1.23	0.22
	Long-term	SPS 3 2012	1.45	1.10	1.93	2.61	0.01
			1.45	1.10	1.93	2.61	0.01



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