## **Supplementary Material**

Antiplatelet Therapy after Aneurysmal Subarachnoid Hemorrhage: A Meta-Analysis

## Supplemental Methodology

Literature Search Details

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Inception to Present - Search ran 04/15/2021

- 1. subarachnoid hemorrhage/
- 2. intracranial hemorrhage/ or cerebral hemorrhage/
- 3. Aneurysm, intracranial/
- 4. Rupture, spontaneous/
- 5. 3 and 4
- 6. Aneurysm, rupture/
- 7. exp brain/ or exp meninges/
- 8. 6 and 7
- 9. ((subarachnoid hemorrhage) adj6 (hemorrhage\$ or bleed\$).tw
- 10. Vasospasm, intracranial/ or ischemia, cerebral/
- 11. ((cerebral or intracranial) adj6 (vasospasm or spasm)).tw.
- 12. sah.tw.
- 13. 1 or 2 or 5 or 8 or 9 or 9 or 10 or 11 or 12
- 14. exp antiplatelet therapy/
- 15. (platelet aggregation inhibitors or anti-platelet).tw.
- 16. (aspirin\$ or acetyl salicylic acid\$ or salicylate\$ or clopidogrel\$ or ticlopidine\$ or dipyridamole\$ or Persantin\$).tw.
- 17. ((glycoprotein iib\$ or gp iib\$ or glycoprotein iiia\$ or gp iiia\$)).tw.
- 18. (abciximab\$ or tirofiban\$ or eptifibatide\$ or ReoPro\$ or prasugrel\$ or ticagrelor\$).tw.
- 19. or/ 14-18
- 20. 13 and 19
- 21. limit 20 to human

The first search was conducted in Ovid MEDLINE. Subject headings and key words were adapted for the other databases.

Supplemental Table I. Rates of Intracranial Hemorrhage in the Included Studies											
	Antiplatel	et Therapy	No Antiplatelet Therapy								
Study (Year)	ICH (%)	Total Population	ICH (%)	Total Population							
Bruder (2018) <sup>1</sup>	6	129	1	129							
Ditz (2021) <sup>2</sup>	5	85	5	75							
Hop (2000) <sup>3</sup>	1	24	2	26							
MASH (Combined											
2009) <sup>4</sup>	2	87	1	74							
Nagahama (2018) <sup>5</sup>	2	85	3	76							
Oppong (2019) <sup>6</sup>	29	329	10	251							
Shaw (1985) <sup>7</sup>	3	173	2	175							
Sun (2020) <sup>8</sup>	5	65	7	101							
Suzuki (1989) <sup>9</sup>	7	172	3	86							
Tokiyoshi (1991) <sup>10</sup>	2	13	0	11							
Total Events	62	1162	34	1004							
Abbreviations: ICH, intrac	ranial hemorrhag	je.									

Supplementary Table I: Results of Risk of Bias Questions to Assess the Quality of Included Studies													
Type of Bias		S	election		De	tection	Attrition	Confounding					
Question:	Was the study sample randomly selected?	Were the inclusion and exclusion criteria adequately described?	Was the primary objective to assess functional outcome?	Was the primary objective to assess DCI?	Was the study prospective in nature?	Were the investigators blinded to the APT status?	Were losses to follow up systematically reported?	Were the data adjusted for covariate risk?					
Bruder (2018) <sup>1</sup>	-	+	+	+	+	-	-	+					
Ditz (2021) <sup>2</sup>	-	+	+	+	-	-	-	+					
Hop (2000) <sup>3</sup>	+	+	+	+	+	+	+	+					
ISAT (2009) <sup>11</sup>	-	+	+	-	-	-	-	+					
Juvela (1995) <sup>12</sup>	-	+	+	+	+	-	-	+					
MASH Clipping (2009) <sup>4</sup>	+	+	+	+	+	+	+	+					
MASH Coiling (2009)) <sup>4</sup>	+	+	+	+	+	+	+	+					
Nagahama (2018) <sup>5</sup>	-	+	+	+	-	-	-	+					
Ono (1984) <sup>13</sup>	+	+	+	+	+	+	+	+					
Oppong (2019) <sup>6</sup>	-	+	+	+	-	-	-	+					
Shaw (1985) <sup>7</sup>	+	+	+	+	+	-	+	+					
Sun (2020) <sup>8</sup>	-	+	+	+	-	-	-	-					
Suzuki (1989) <sup>9</sup>	+	+	+	+	+	+	+	+					
Tokiyoshi (1991) <sup>10</sup>	+	+	+	+	+	+	+	+					
Toussaint (2004) <sup>14</sup>	-	+	+	+	-	-	-	+					
Abbreviations: IC	H, intracrani	al hemorrhage	)										

## Supplemental Figure I: Study selection flow diagram



**Supplemental Figure II:** Funnel Plot to Evaluate Publication Bias of Functional Outcome after Subarachnoid Hemorrhage.



Supplemental Figure III: Funnel Plot to Evaluate Publication Bias of Delayed Cerebral Ischemia after Subarachnoid Hemorrhage.



**Supplemental Figure IV:** Funnel Plot to Evaluate Publication Bias of Intracranial Hemorrhage after Subarachnoid Hemorrhage.



**Supplemental Figure V.** Forest plot of the association between antiplatelet therapy and good functional outcome after aneurysmal subarachnoid hemorrhage, stratified by type of antiplatelet medication.

Study	Trea Events	tment Total	C Events	ontrol Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
Aspirin and/or clopidog Bruder Ditz Hop Juvela MASH Clipping MASH Colling Nagahama Oppong Toussaint Fixed effect model Random effects model Heterogeneity: 1 <sup>2</sup> = 35%, τ <sup>2</sup>	71 62 18 40 40 28 77 169 19 530	144 85 24 58 53 33 85 230 29 741 4, p = 0	75 41 16 66 46 15 63 120 185 <b>627</b> 0.14	144 75 26 144 55 19 76 192 276 1007		0.95 1.33 1.22 - 1.50 1.04 1.07 1.09 1.18 0.98 1.12 1.13	[0.75; 1.19] [1.05; 1.70] [0.83; 1.79] [1.17; 1.93] [0.89; 1.21] [0.82; 1.41] [0.97; 1.24] [1.03; 1.34] [0.74; 1.29] [1.05; 1.20] [1.04; 1.23]	3.5% 3.1% 1.3% 3.0% 7.5% 2.5% 12.2% 10.2% 2.4% 45.6%	5.5% 5.0% 2.4% 4.9% 8.7% 4.2% 11.0% 4.2% 10.2% 4.1% 56.0%
Dipyridamole Shaw Fixed effect model Random effects model Heterogeneity: not applicat	100 100	173 173	105 105	175 175		0.96 0.96 0.96	[0.81; 1.15] [0.81; 1.15] [0.81; 1.15]	6.0% 6.0% 	7.7%  7.7%
Ticlopidine Ono Fixed effect model Random effects model Heterogeneity: not applicat	60 60	65 65	54 54	68 68		1.16 1.16 1.16	[1.01; 1.34] [1.01; 1.34] [1.01; 1.34]	9.4% 9.4% 	9.8%  9.8%
Ozagrel Tokiyoshi Fixed effect model Random effects model Heterogeneity: not applicat	11 11	13 13	8 8	11 11		1.16 1.16 1.16	[0.76; 1.79] [0.76; 1.79] [0.76; 1.79]	1.0% 1.0% 	2.0%  2.0%
OKY-046 Suzuki Fixed effect model Random effects model Heterogeneity: not applicat	137 137	170 170	68 68	86 86		1.02 1.02 1.02	[0.89; 1.16] [0.89; 1.16] [0.89; 1.16]	10.7% 10.7% 	10.4%  10.4%
Unspecified ISAT Fixed effect model Random effects model Heterogeneity: not applicat	228 228	331 331	755 755	1064 1064	\$ \$ \$	0.97 0.97 0.97	[0.89; 1.05] [0.89; 1.05] [0.89; 1.05]	27.4% 27.4% 	14.2%  14.2%
Fixed effect model Random effects model Heterogeneity: $I^2 = 44\%$ , $\tau^2$	<b>1066</b> <sup>2</sup> = 0.005	<b>1493</b> 7, ρ = 0	<b>1617</b> 0.04	2411	0.75 1 1.5	1.06 1.08	[1.02; 1.11] [1.02; 1.15]	100.0% 	 100.0%

**Supplemental Figure VI.** Forest plot of the association between antiplatelet therapy and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage, stratified by type of antiplatelet medication.

Treatment Control							Weight	Weight	
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
Aspirin and/or clopidog	rel				1				
Bruder	57	144	54	144	al.	1.06	[0.79: 1.41]	16.6%	14.4%
Ditz	21	85	20	75		0.93	[0.55; 1.57]	5.1%	9.6%
Нор	4	24	4	26	<u>2</u>	1.08	[0.30; 3.86]	0.9%	2.9%
ISAT	93	331	319	1064	+	0.94	[0.77; 1.14]	37.2%	16.4%
Juvela	22	50	40	88		0.97	[0.66; 1.43]	9.4%	12.4%
MASH Clipping	15	53	9	55		1.73	[0.83; 3.61]	2.6%	6.7%
MASH Coiling	5	33	2	19		1.44	[0.31; 6.71]	0.6%	2.1%
Nagahama	3	85	17	76	i  (	0.16	[0.05; 0.52]	1.0%	3.3%
Oppong	52	299	68	225	-=	0.58	[0.42; 0.79]	14.1%	13.9%
Sun	1	65	11	101 ·		0.14	[0.02; 1.07]	0.3%	1.3%
Toussaint	3	13	46	92		0.46	[0.17; 1.27]	1.4%	4.2%
Fixed effect model	276	1182	590	1965	\$	0.88	[0.77; 0.99]	89.3%	
Random effects model					<b>4</b>	0.83	[0.64; 1.07]		87.1%
Heterogeneity: $I^2 = 61\%$ , $\tau^2$	= 0.085	5, p < 0	0.01		a a				
Ticlopidine					a a				
Suzuki	38	121	31	63		0 64	[0 44· 0 92]	10 7%	12 9%
Fixed effect model	38	121	31	63		0.64	[0.44: 0.92]	10.7%	
Random effects model					Š.	0.64	[0.44: 0.92]		12.9%
Heterogeneity: not applicab	le						. / 4		
<b>-</b>		4000			1			400.00	
Fixed effect model	314	1303	621	2028		0.85	[0.75; 0.95]	100.0%	
Random effects model						0.80	[0.63; 1.02]		100.0%
Heterogeneity: $I^2 = 61\%$ , $\tau^2$	= 0.080	J, p < (	J.U1		0.1 0.5.1 0 10				
					0.1 0.51 2 10				

**Supplemental Figure VII.** Forest plot of the association between antiplatelet therapy and intracranial hemorrhage after aneurysmal subarachnoid hemorrhage, stratified by type of antiplatelet medication.

	Trea	tment	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
Aspirin and/or clopidog Bruder Ditz Hop MASH (combined) Nagahama Oppong Sun Fixed effect model Random effects model Heterogeneity: /² = 0%, τ²	rel 6 5 1 2 29 5 50 = 0, p = (	129 85 24 87 85 329 65 804	1 5 2 1 3 10 7 29	129 75 26 74 76 251 101 732		6.00 0.88 0.54 1.70 0.60 2.21 1.11 1.51	[0.73; 49.14] [0.27; 2.93] [0.05; 5.60] [0.16; 18.39] [0.10; 3.47] [1.10; 4.45] [0.37; 3.35] [0.94; 2.42] [0.94; 2.42]	4.1% 12.7% 3.4% 3.2% 5.9% 37.4% 15.0% 81.7%	4.1% 12.7% 3.4% 5.9% 37.4% 15.0% 81.7%
Dipyridamole Shaw Fixed effect model Random effects model Heterogeneity: not applicat	3 3	173 173	2	175 175		1.52 1.52 1.52	[0.26; 8.97] [0.26; 8.97] [0.26; 8.97]	5.8% 5.8% 	5.8%  5.8%
OKY-046 Suzuki Fixed effect model Random effects model Heterogeneity: not applicat	7 7	172 172	3 3	86 86		1.17 1.17 1.17	[0.31; 4.40] [0.31; 4.40] [0.31; 4.40]	10.4% 10.4% 	10.4%  10.4%
Ozagrel Tokiyoshi Fixed effect model Random effects model Heterogeneity: not applicat	2 2	13 13	0	11 11		- 4.26 - 4.26 - 4.26	[0.23; 79.98] [0.23; 79.98] [0.23; 79.98]	2.1% 2.1% 	2.1%  2.1%
Fixed effect model Random effects model Heterogeneity: $I^2 = 0\%$ , $\tau^2$	<b>62</b> = 0, <i>p</i> = 0	<b>1162</b> 0.71	34	1004	0.1 0.51 2 10	1.50 1.50	[0.98; 2.31] [0.98; 2.31]	100.0% 	 100.0%

Supplemental Figure VIII. Forest plot of the association between antiplatelet therapy

and functional outcome after aneurysmal subarachnoid hemorrhage, stratified by study

type.

	Trea	tment	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio F	RR	95%-CI	(fixed)	(random)
RCT									
Нор	18	24	16	26		22	[0.83; 1.79]	1.3%	2.4%
ISAT	228	331	755	1064	0.	97	[0.89; 1.05]	27.4%	14.2%
MASH Clipping	46	53	46	55		04	[0.89; 1.21]	7.5%	8.7%
MASH Coiling	28	33	15	19		07	[0.82; 1.41]	2.5%	4.2%
Ono	60	65	54	68	1.	16	[1.01; 1.34]	9.4%	9.8%
Shaw	100	173	105	175		96	[0.81; 1.15]	6.0%	7.7%
Suzuki	137	170	68	86	<u>– – – 1.</u>	02	[0.89; 1.16]	10.7%	10.4%
Fixed effect model	617	849	1059	1493	<b>4</b> 1.	02	[0.97; 1.08]	64.6%	
Random effects model					🔶 1.	02	[0.97; 1.08]		57.4%
Heterogeneity: $I^2 = 3\%$ , $\tau^2$	= 0.0002	p = 0.	40						
Prospective									
Bruder	71	144	75	144		95	[0.75; 1.19]	3.5%	5.5%
Juvela	40	58	66	144	1.	50	[1.17; 1.93]	3.0%	4.9%
Tokiyoshi	11	13	8	11		16	[0.76; 1.79]	1.0%	2.0%
Fixed effect model	122	215	149	299	1.	17	[1.00; 1.37]	7.5%	
Random effects model					1.	18	[0.86; 1.62]		12.3%
Heterogeneity: $I^2 = 73\%$ , $\tau$	<sup>2</sup> = 0.055	6, p = (	0.03						
Retrospective									
Ditz	62	85	41	75	1.	33	[1.05; 1.70]	3.1%	5.0%
Nagahama	77	85	63	76	1.	09	[0.97; 1.24]	12.2%	11.0%
Oppong	169	230	120	192	1.	18	[1.03; 1.34]	10.2%	10.2%
Toussaint	19	29	185	276		98	[0.74; 1.29]	2.4%	4.1%
Fixed effect model	327	429	409	619	► 1.	14	[1.05; 1.23]	27.9%	
Random effects model					۵. ایک	14	[1.04; 1.25]		30.3%
Heterogeneity: $I^2 = 13\%$ , $\tau$	<sup>2</sup> = 0.001	2, p = (	0.33						
Fixed effect model	1066	1493	1617	2411	l 🔶 1.	06	[1.02; 1.11]	100.0%	
Random effects model	2				<u> </u>	08	[1.02; 1.15]		100.0%
Heterogeneity: $I^2 = 44\%$ , $\tau$	= 0.005	7, p = 0	0.04		1 1 1				
					0.75 1 1.5				

**Supplemental Figure IX.** Forest plot of the association between antiplatelet therapy and delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage, stratified by study type.

Study	Treat Events	tment Total	Co Events	ontrol Total	Risk Ratio	RR	95%-CI	Weight	Weight (random)
<b>,</b>								(	(,
RCT					3				
Нор	4	24	4	26		1.08	[0.30; 3.86]	0.9%	2.9%
ISAT	93	331	319	1064		0.94	[0.77; 1.14]	37.2%	16.4%
MASH Clipping	15	53	9	55	<u></u>	1.73	[0.83; 3.61]	2.6%	6.7%
MASH Coiling	5	33	2	19		1.44	[0.31; 6.71]	0.6%	2.1%
Suzuki	38	121	31	63	- <del></del>	0.64	[0.44; 0.92]	10.7%	12.9%
Fixed effect model	155	562	365	1227	è	0.90	[0.76; 1.06]	52.0%	
Random effects model					÷,	0.93	[0.67; 1.27]		40.9%
Heterogeneity: $I^2 = 43\%$ , $\tau$	<sup>2</sup> = 0.0491	I, p = 0	0.13		a a				
					2				
Prospective									
Bruder	57	144	54	144	テレー	1.06	[0.79; 1.41]	16.6%	14.4%
Juvela	22	50	40	88	<del></del>	0.97	[0.66; 1.43]	9.4%	12.4%
Fixed effect model	79	194	94	232	<u>له</u>	1.02	[0.81; 1.29]	26.1%	
Random effects model					於	1.02	[0.81; 1.29]		26.8%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	.73			a				
					5				
Retrospective					a				
Ditz	21	85	20	75		0.93	[0.55; 1.57]	5.1%	9.6%
Nagahama	3	85	17	76	à	0.16	[0.05; 0.52]	1.0%	3.3%
Oppong	52	299	68	225	- <b>-</b>	0.58	[0.42; 0.79]	14.1%	13.9%
Sun	1	65	11	101 ·	+ <u>a</u>	0.14	[0.02; 1.07]	0.3%	1.3%
Toussaint	3	13	46	92		0.46	[0.17; 1.27]	1.4%	4.2%
Fixed effect model	80	547	162	569		0.58	[0.45; 0.75]	21.9%	
Random effects model	2					0.49	[0.29; 0.84]		32.3%
Heterogeneity: $I^2 = 59\%$ , $\tau$	÷ = 0.1826	6, p = 0	0.05		a				
					ä				
Fixed effect model	314	1303	621	2028		0.85	[0.75; 0.95]	100.0%	
Random effects model	2					0.80	[0.63; 1.02]		100.0%
Heterogeneity: $I^{2} = 61\%$ , $\tau$	~ = 0.0800	), p < (	J.01		04 054 0 10				
					0.1 0.5 1 2 10				

**Supplemental Figure X.** Forest plot of the association between antiplatelet therapy and intracranial hemorrhage after aneurysmal subarachnoid hemorrhage, stratified by study type.

	Trea	tment	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
RCT									
Нор	1	24	2	26		.54	[0.05; 5.60]	3.4%	3.4%
MASH (combined)	2	87	1	74	1	.70	[0.16; 18.39]	3.2%	3.2%
Shaw	3	173	2	175		.52	[0.26; 8.97]	5.8%	5.8%
Suzuki	7	172	3	86		.17	[0.31; 4.40]	10.4%	10.4%
Fixed effect model	13	456	8	361	1	.18	[0.48: 2.88]	22.8%	
Random effects model					1	.18	[0.48; 2.88]		22.8%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	0.90					n / a		
Brooppostivo									
Prospective	0	100	4	100		00	10 72. 40 441	4 4 0/	4 4 0/
Bruder Taliwashi	0	129	1	129	0	.00	[0.73, 49.14]	4.1%	4.1%
	2	13	0	110	4	.20	[0.23; 79.98]	2.1%	2.1%
Fixed effect model	8	142	.1	140	5	.34	[0.97; 29.50]	6.3%	0.00/
Random effects model					5	.34	[0.97; 29.50]		6.3%
Heterogeneity: $I = 0\%$ , $\tau$	= 0, p = 0	1.85							
Retrospective									
Ditz	5	85	5	75		.88.	[0.27; 2.93]	12.7%	12.7%
Nagahama	2	85	3	76		.60	[0.10; 3.47]	5.9%	5.9%
Oppong	29	329	10	251	2	.21	[1.10; 4.45]	37.4%	37.4%
Sun	5	65	7	101		.11	[0.37; 3.35]	15.0%	15.0%
Fixed effect model	41	564	25	503	1	.45	[0.88; 2.42]	71.0%	
Random effects model					1	.41	[0.82; 2.43]		71.0%
Heterogeneity: $I^2 = 8\%$ , $\tau^2$	= 0.0274	p = 0.	35						
Fixed effect model	62	1162	34	1004	i 🔶 1.	.50	[0.98; 2.31]	100.0%	
Random effects model						.50	[0.98; 2.31]		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$	= 0, p = 0	0.71							
					01 051 2 10				

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