Supplementary Online Content

Antithrombotic Regimens for the Prevention of Major Adverse Cardiac Events in Patients with Chronic Coronary Syndrome - A Systematic Review and Network Meta-Analysis

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Systematic Review

Search Strategies

Database	Terms
PubMed	("Arteriosclerosis"[mh] OR "Angina, Stable"[mh]) AND ("Platelet Aggregation Inhibitors" [Mesh] OR "Dual Anti-Platelet Therapy" [Mesh] OR "Aspirin"[mh] OR "Clopidogrel"[mh] OR "Factor Xa Inhibitors"[mh] OR "apixaban"[Supplementary Concept] OR "edoxaban"[Supplementary Concept] OR "Rivaroxaban"[mh] OR "Purinergic P2Y Receptor Antagonists"[mh] OR "Ticagrelor"[mh] OR "Prasugrel"[tw] OR "Vorapaxar"[tw]) AND ("Myocardial Infarction"[mh] OR "Angina, Unstable"[mh] OR "Stroke"[Mesh] OR Death, Sudden, Cardiac [Mesh] OR "Myocardial Revascularization"[mh] OR "Major Adverse Cardiac Event"[tw] OR "Hemorrhage"[mh])
EMBASE	('atherosclerosis'/exp OR 'stable angina pectoris'/exp) AND ('antithrombocytic agent'/exp OR 'dual antiplatelet therapy'/exp OR 'acetylsalicylic acid'/mj OR 'clopidogrel'/mj OR 'blood clotting factor 10a inhibitor'/exp OR 'apixaban'/mj OR 'edoxaban'/mj OR 'rivaroxaban'/mj OR 'purinergic p2y receptor antagonist'/exp OR 'ticagrelor'/mj OR 'prasugrel'/mj OR 'vorapaxar'/mj) AND ('heart infarction'/mj OR 'unstable angina pectoris'/mj OR 'cerebrovascular accident'/mj OR 'heart muscle revascularization'/exp OR 'major adverse cardiac event'/mj OR 'bleeding'/exp)
CENTRAL	/#1 MeSH descriptor: [Arteriosclerosis] explode all trees 11018 /#2 MeSH descriptor: [Angina, Stable] explode all trees 360 /#3 #1 OR #2 11264 /#4 MeSH descriptor: [Platelet Aggregation Inhibitors] explode all trees 4016 /#5 MeSH descriptor: [Dual Anti-Platelet Therapy] explode all trees 45 /#6 MeSH descriptor: [Aspirin] explode all trees 6018 /#7 MeSH descriptor: [Clopidogrel] explode all trees 2074 /#8 MeSH descriptor: [Factor Xa Inhibitors] explode all trees 572 /#9 (apixaban):ti,ab,kw 984 /#10 (edoxaban):ti,ab,kw 598 /#11 MeSH descriptor: [Rivaroxaban] explode all trees 568 /#12 MeSH descriptor: [Purinergic P2Y Receptor Antagonists] explode all trees 359 /#13 MeSH descriptor: [Ticagrelor] explode all trees 786 /#14 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 10962 /#15 MeSH descriptor: [Myocardial Infarction] explode all trees 11333 /#16 MeSH descriptor: [Angina, Unstable] explode all trees 1138 /#17 MeSH descriptor: [Stroke] explode all trees 10342 /#18 MeSH descriptor: [Death, Sudden, Cardiac] explode all trees 635 /#19 MeSH descriptor: [Myocardial Revascularization] explode all trees 9254 /#20 (Major Adverse Cardiac Event):ti,ab,kw 2745 /#21 MeSH descriptor: [Hemorrhage] explode all trees 14754 /#22 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 43672 **/#23 #3 AND #14 AND #22**

eTable 1: Trial definitions

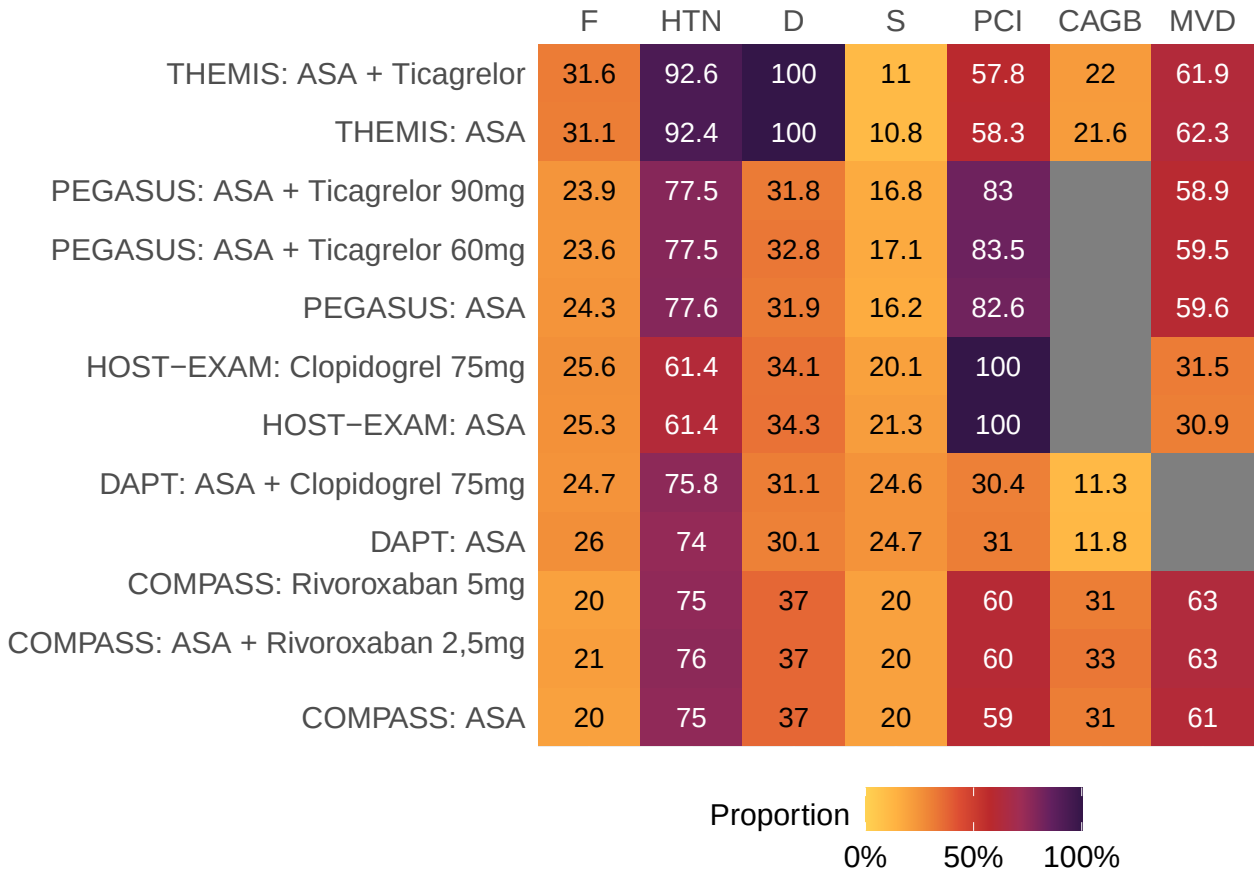
Study	MACE trial definition	Safety endpoint definition
DAPT	Composite of death, myocardial infarction, or stroke during the randomized treatment period month 12 to month 30.	Incidence of moderate or severe bleeding during the randomized treatment period month 12 to month 30 assessed according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries [GUSTO] criteria.*
COMPASS	Composite of cardiovascular death, stroke, or myocardial infarction.	Modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay). Unlike the ISTH criteria, we considered all bleeding that led to presentation to an acute care facility or hospitalization as major.
HOST-EXAM	Composite of cardiac death, non-fatal myocardial infarction, ischaemic stroke, readmission due to acute coronary syndrome, and definite or probable stent thrombosis (originally referred to as "thrombotic composite outcome").	Major bleeding, that was defined as Bleeding Academic Research Consortium (BARC) type bleeding of least 3.**
THEMIS	Composite of cardiovascular death, myocardial infarction, or stroke.	TIMI major bleeding. ***
PEGASUS	Composite of cardiovascular death, myocardial infarction, or stroke.	Major bleeding, which was defined according to the TIMI classification.***

* Moderate bleeding is defined as bleeding requiring blood transfusion, but not resulting in hemodynamic compromise, and severe bleeding is defined as either an intracerebral hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment according to the GUSTO criteria.

** BARC type bleeding of 3 is defined as clinical, laboratory, and/or imaging evidence of bleeding with healthcare responses, as listed: Any transfusion with overt bleeding; Overt bleeding plus hemoglobin (Hb) drop >=3 to <5 g/dI (provided Hb drop is related to bleeding); Overt bleeding plus Hb drop >=5 g/dl; Cardiac tamponade; Bleeding requiring surgical intervention for control; Bleeding requiring intravenous vasoactive drugs; Intracranial hemorrhage; Intraocular bleed compromising vision.

*** TIMI major bleeding is defined as any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI), or clinically overt signs of hemorrhage associated with a drop in hemoglobin of >=5 g/dL or a >=15% absolute decrease in haematocrit, or a fatal bleeding (bleeding that directly results in death within 7 d).

eFigure 1: Effect Modifiers



Heatmap on the proportions of potential efffect modifiers across included studies and treatment arms. Each row corresponds to a specific study and treatment arm combination. Each column corresponds to a specific effect modifier. The exact proportion is depicted by both filled color and the number on top in each cell.

Abbreviations: F, female; HTN, hypertension; D, diabetes; S, smoker; PCI, percutaneous coronary intervention; CAGB, coronary artery bypass graft; MVD, multivessel disease.

eTable 2: Risk of Bias Assessment

Risk of bias for domain-level as well as overall judgements.

D1: bias arising from randomisation process; D2: bias arising from deviations from intended interventions; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result.

MACE

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Ticagrelor 60mg vs.ASA	Low	Low	Low	Low	Low	Low
THEMIS, ASA + Ticagrelor 90mg vs.ASA	Low	Low	Low	Low	Low	Low
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Ticagrelor 60mg vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Ticagrelor 90mg vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

Bleeding

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Ticagrelor 60mg vs.ASA	Low	Low	Low	Low	Low	Low
THEMIS, ASA + Ticagrelor 90mg vs.ASA	Low	Low	Low	Low	Low	Low
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Ticagrelor 60mg vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Ticagrelor 90mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Some concerns	Low	Some concerns
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Some concerns	Low	Some concerns
HOSTEXAM, Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

Acute Myocardial Infarction

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Low	Low	Low
HOSTEXAM, Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

Ischemic Stroke

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Low	Low	Low
HOSTEXAM, Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

All-cause Mortality

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Low	Low	Low
HOSTEXAM, Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

Cardiovascular Mortality

Study, Comparison	D1	D2	D3	D4	D5	Overall
THEMIS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
PEGASUS, ASA + Pooled Ticagrelor vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, ASA + Rivaroxaban 2.5mg vs.ASA	Low	Low	Low	Low	Low	Low
COMPASS, Rivaroxaban 5mg vs.ASA	Low	Low	Low	Low	Low	Low
HOSTEXAM, Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low
DAPT, ASA + Prasugrel 10mg or Clopidogrel 75mg vs.ASA	Low	Low	Low	Low	Low	Low

Pooled Ticagrelor Networks: MACE and Bleeding Outcomes

League Tables

eTable 3: Median and 95% Credible Intervals

ASA	0.89 (0.78, 1.02)	0.68 (0.54, 0.88)	0.74 (0.65, 0.86)	0.52 (0.39, 0.71)	0.80 (0.64, 1.00)	0.87 (0.81, 0.94)
1.47 (0.94, 2.21)	Rivaroxaban 5mg	0.76 (0.57, 1.01)	0.83 (0.73, 0.96)	0.59 (0.42, 0.81)	0.90 (0.70, 1.18)	0.98 (0.84, 1.14)
0.64 (0.42, 0.99)	0.44 (0.24, 0.77)	Clopidogrel 75mg	1.09 (0.81, 1.44)	0.77 (0.52, 1.15)	1.18 (0.85, 1.66)	1.28 (0.97, 1.64)
1.01 (0.64, 1.61)	0.69 (0.44, 1.09)	1.58 (0.85, 2.97)	ASA + Rivaroxaban 2.5mg	0.71 (0.50, 0.99)	1.08 (0.83, 1.42)	1.18 (1.01, 1.38)
1.71 (1.02, 2.95)	1.16 (0.60, 2.34)	2.67 (1.33, 5.18)	1.68 (0.84, 3.39)	ASA + Prasugrel 10mg	1.53 (1.18, 1.97)	1.67 (1.19, 2.24)
1.53 (1.05, 2.14)	1.04 (0.58, 1.77)	2.39 (1.37, 4.22)	1.50 (0.82, 2.64)	0.89 (0.60, 1.40)	ASA + Clopidogrel 75mg	1.09 (0.87, 1.40)
2.40 (2.06, 2.83)	1.63 (1.04, 2.59)	3.76 (2.42, 6.14)	2.37 (1.45, 3.85)	1.41 (0.80, 2.43)	1.58 (1.07, 2.36)	Pooled Ticagrelor

Hazard ratios (95% credible interval) for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, the corresponding HR (95% CrI) was 0.89 (0.78, 1.02), favoring Rivaroxaban 5mg (ie, HR < 1.0).

eTable 4: Posterior Probabilities of Hazard Ratio < 1.0

ASA	95.31	99.88	100.00	100.00	97.26	100.00
3.92	Rivaroxaban 5mg	96.90	99.54	99.91	78.17	61.26
97.92	99.76	Clopidogrel 75mg	28.56	89.94	16.98	3.16
47.45	94.46	7.05	ASA + Rivaroxaban 2.5mg	97.74	27.98	2.17
2.57	33.59	0.25	7.61	ASA + Prasugrel 10mg	0.00	0.06
1.03	44.61	0.05	8.58	69.67	ASA + Clopidogrel 75mg	25.49
0.00	1.73	0.00	0.05	11.50	1.25	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 1.0 for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 95.31% that the hazard ratio is below 1.0 (ie, there was a 95.31% probability for Rivaroxaban 5mg superiority).

eTable 5: Posterior Probabilities of Hazard Ratio < 0.8

ASA	5.58	89.61	85.65	99.66	48.62	1.16
0.35	Rivaroxaban 5mg	62.45	29.80	96.12	18.44	0.56
85.04	97.92	Clopidogrel 75mg	1.82	57.90	1.14	0.01
15.74	73.61	1.47	ASA + Rivaroxaban 2.5mg	75.70	1.14	0.00
0.24	14.39	0.04	2.01	ASA + Prasugrel 10mg	0.00	0.00
0.05	18.09	0.00	1.71	29.99	ASA + Clopidogrel 75mg	0.64
0.00	0.06	0.00	0.00	2.23	0.05	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 0.8 for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 5.58% that the hazard ratio is below 0.8 (ie, there was a 5.58% probability for Rivaroxaban 5mg superiority).

eTable 6: Posterior Probabilities of Hazard Ratio > 1.25

ASA	0.00	0.00	0.00	0.00	0.01	0.00
76.95	Rivaroxaban 5mg	0.03	0.00	0.00	0.57	0.07
0.05	0.00	Clopidogrel 75mg	17.11	0.94	36.49	57.04
18.64	0.59	76.92	ASA + Rivaroxaban 2.5mg	0.05	14.91	22.07
87.24	41.85	98.52	79.15	ASA + Prasugrel 10mg	93.88	95.88
86.21	25.57	98.76	72.86	6.39	ASA + Clopidogrel 75mg	12.20
100.00	87.86	100.00	99.36	66.38	87.86	Pooled Ticagrelor

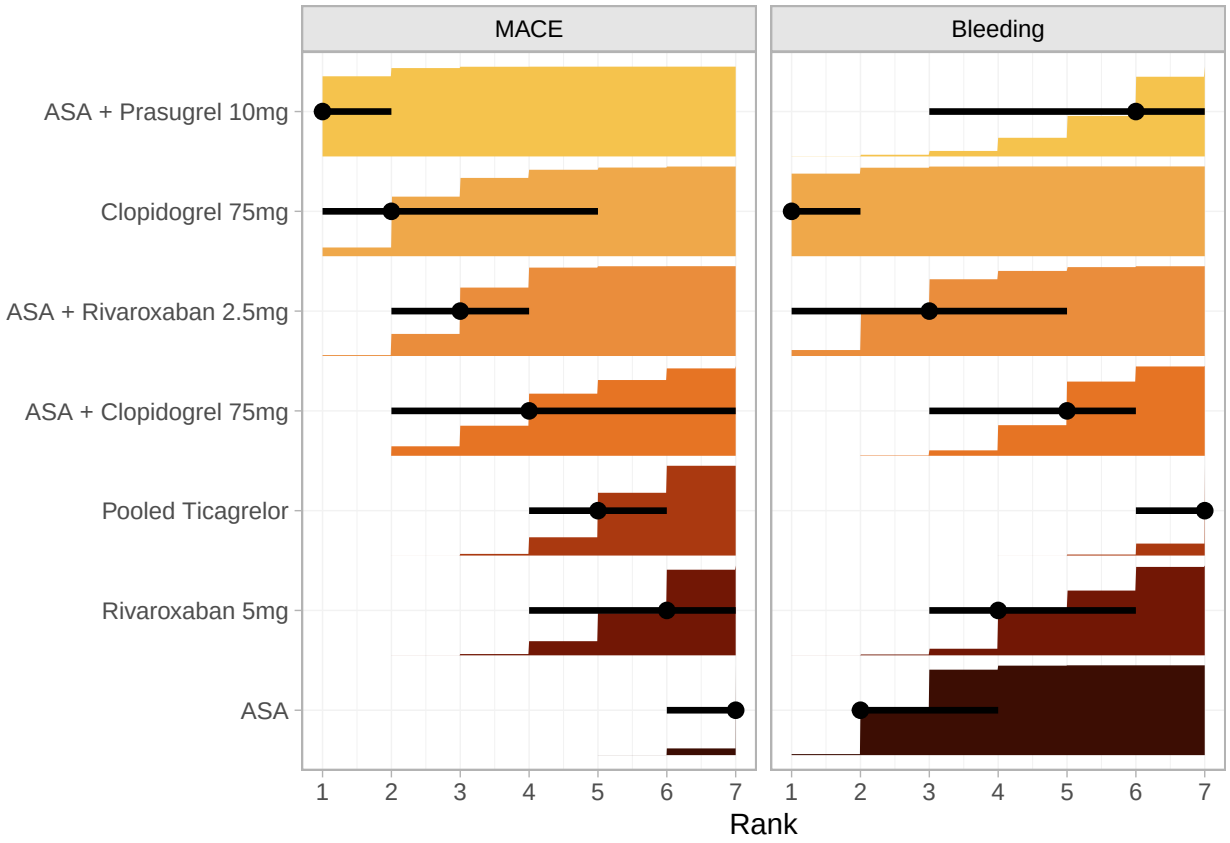
Posterior probabilities (%) of hazard ratio > 1.25 for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 0.00% that the hazard ratio is above 1.25.

eTable 7: Posterior Probabilities of Hazard Ratio within the ROPE

ASA	94.42	10.39	14.35	0.34	51.36	98.84
22.70	Rivaroxaban 5mg	37.52	70.20	3.88	80.99	99.36
14.91	2.08	Clopidogrel 75mg	81.06	41.16	62.38	42.95
65.62	25.80	21.60	ASA + Rivaroxaban 2.5mg	24.25	83.95	77.92
12.53	43.76	1.44	18.84	ASA + Prasugrel 10mg	6.12	4.12
13.74	56.34	1.24	25.42	63.62	ASA + Clopidogrel 75mg	87.16
0.00	12.07	0.00	0.64	31.40	12.09	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio within the region of practical equivalence (ROPE), ie, between 0.80 and 1.25, for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 94.42% that the hazard ratio is within the ROPE.

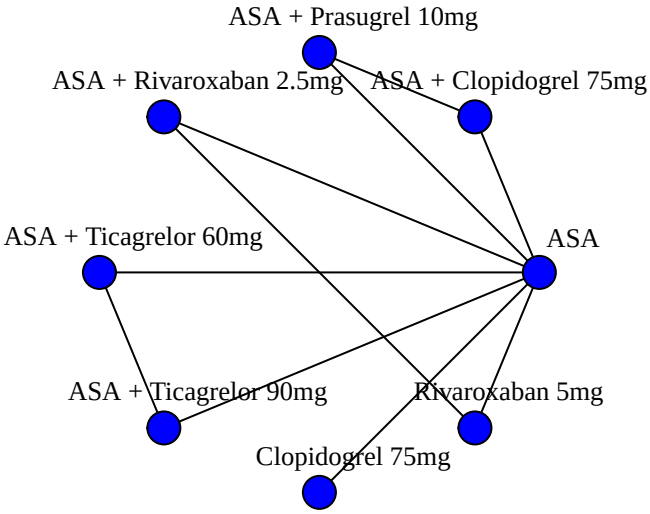
eFigure 2: Ranks with Uncertainty



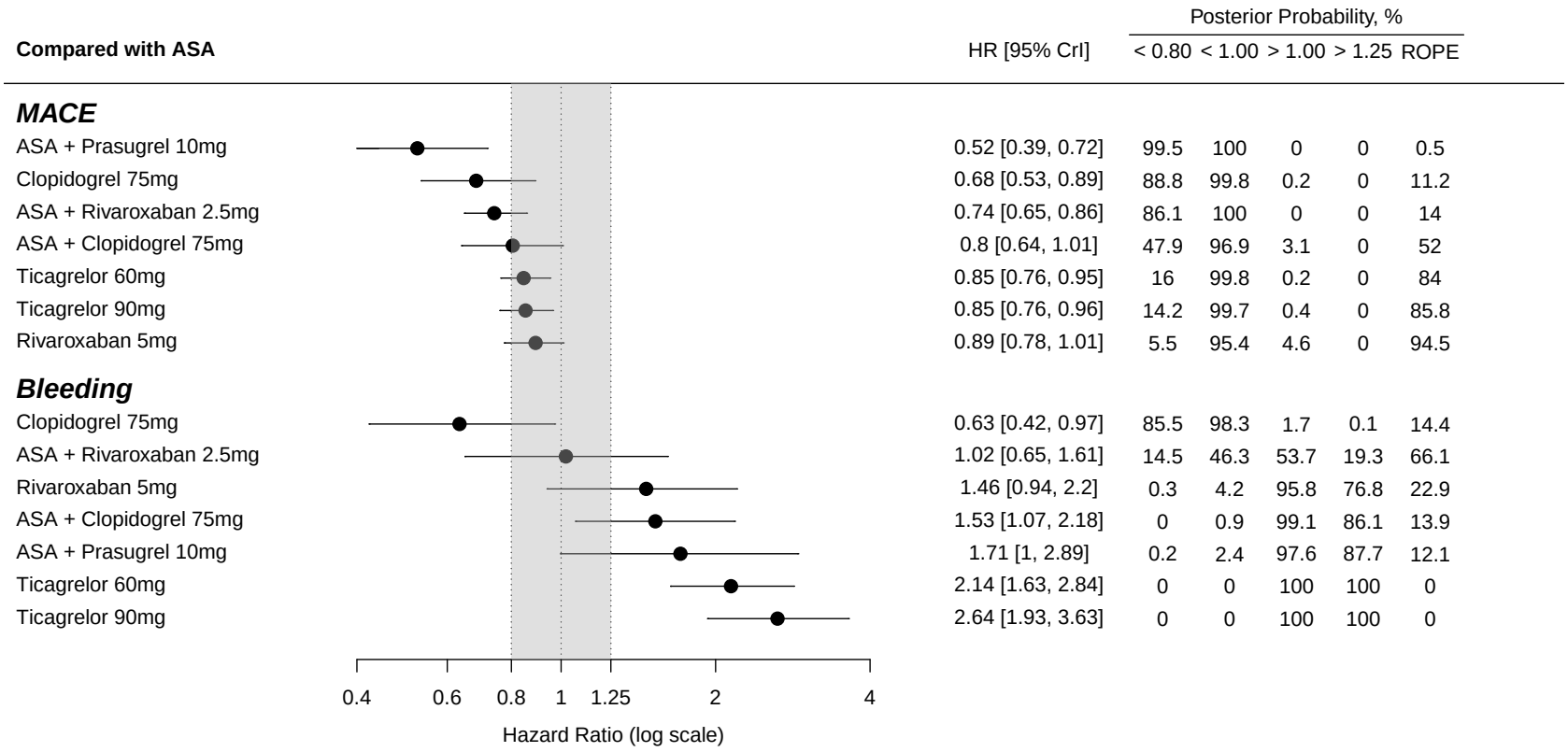
Marginal posterior distributions for the rank of each treatment. Left panel depicts ranks for MACE, while right panel for the Bleeding outcome. In each panel, there are a point estimate, interval bar, and bar plot for each treatment (Y-axis). The point estimate represents the median rank. The interval bar shows the 95% credible (quantile) interval of the underlying marginal posterior distribution. Lastly, the bar plot shows the cumulative distribution function (CDF).

Separate Dosages Ticagrelor Networks: MACE and Bleeding Outcomes

eFigure 3: Network Plot



eFigure 4: Forest Plot



Left panel: Network of MACE and Bleeding outcomes while separing Ticagrelor's dosages. Right panel: Treatment effects compared to ASA on MACE and Bleeding outcomes, ordered according to underlying SUCRA values. HR below 1.0 favors the experimental treatment. On the left, treatment names are depicted. In the middle, forest plot shows each treatment effect median and 95% credible intervals. Gray area corresponds to the ROPE (from 0.8 to 1.25 HR). On the right, exact effect sizes along with posterior probabilities are shown. Abbreviations: ROPE, region of practical equivalence; HR, hazard ratio.

League Tables

eTable 8: Median and 95% Credible Intervals

ASA	0.89 (0.78, 1.01)	0.85 (0.76, 0.95)	0.68 (0.53, 0.89)	0.85 (0.76, 0.96)	0.74 (0.65, 0.86)	0.52 (0.39, 0.72)	0.80 (0.64, 1.01)
1.46 (0.94, 2.20)	Rivaroxaban 5mg	0.95 (0.80, 1.14)	0.77 (0.58, 1.02)	0.96 (0.79, 1.14)	0.83 (0.72, 0.95)	0.59 (0.42, 0.83)	0.90 (0.69, 1.17)
2.14 (1.63, 2.84)	1.46 (0.88, 2.46)	Ticagrelor 60mg	0.81 (0.61, 1.07)	1.01 (0.90, 1.14)	0.88 (0.73, 1.04)	0.62 (0.45, 0.87)	0.95 (0.74, 1.22)
0.63 (0.42, 0.97)	0.43 (0.24, 0.80)	0.30 (0.18, 0.49)	Clopidogrel 75mg	1.25 (0.94, 1.66)	1.09 (0.81, 1.45)	0.77 (0.52, 1.16)	1.18 (0.83, 1.65)
2.64 (1.93, 3.63)	1.80 (1.07, 3.14)	1.23 (0.83, 1.86)	4.17 (2.46, 6.83)	Ticagrelor 90mg	0.87 (0.72, 1.04)	0.61 (0.45, 0.88)	0.94 (0.73, 1.23)
1.02 (0.65, 1.61)	0.70 (0.38, 1.28)	0.48 (0.28, 0.81)	1.61 (0.87, 2.97)	0.39 (0.23, 0.68)	ASA + Rivaroxaban 2.5mg	0.71 (0.51, 1.01)	1.08 (0.84, 1.42)
1.71 (1.00, 2.89)	1.17 (0.60, 2.28)	0.80 (0.44, 1.43)	2.68 (1.40, 5.31)	0.64 (0.35, 1.22)	1.68 (0.86, 3.35)	ASA + Prasugrel 10mg	1.54 (1.18, 1.97)
1.53 (1.07, 2.18)	1.04 (0.57, 1.74)	0.71 (0.45, 1.10)	2.41 (1.33, 4.10)	0.58 (0.37, 0.93)	1.50 (0.84, 2.66)	0.90 (0.51, 1.61)	ASA + Clopidogrel 75mg

Hazard ratios (95% credible interval) for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, the corresponding HR (95% CrI) was 0.89 (0.78, 1.01), favoring Rivaroxaban 5mg (ie, HR < 1.0).

eTable 9: Posterior Probabilities of Hazard Ratio < 1.0

ASA	95.41	99.83	99.80	99.65	100.00	100.00	96.94
4.19	Rivaroxaban 5mg	72.45	96.55	68.62	99.60	99.81	77.71
0.00	7.22	Ticagrelor 60mg	93.51	44.66	92.74	99.75	65.62
98.30	99.67	100.00	Clopidogrel 75mg	6.05	29.04	89.31	17.41
0.00	1.74	15.07	0.00	Ticagrelor 90mg	93.29	99.72	67.73
46.27	87.56	99.69	6.48	99.95	ASA + Rivaroxaban 2.5mg	97.45	27.45
2.43	32.60	76.79	0.10	91.61	7.49	ASA + Prasugrel 10mg	0.04
0.86	44.02	92.47	0.09	98.98	8.45	64.12	ASA + Clopidogrel 75mg

Hazard ratios (95% credible interval) for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, the corresponding HR (95% CrI) was 95.41, favoring Rivaroxaban 5mg (ie, HR < 1.0).

eTable 10: Posterior Probabilities of Hazard Ratio < 0.8

ASA	5.53	16.05	88.83	14.24	86.05	99.50	47.95
0.27	Rivaroxaban 5mg	2.69	61.99	2.41	28.99	96.06	18.36
0.00	1.16	Ticagrelor 60mg	47.15	0.00	15.75	93.44	8.50
85.49	97.67	100.00	Clopidogrel 75mg	0.11	1.98	56.94	1.32
0.00	0.14	1.93	0.00	Ticagrelor 90mg	19.01	94.04	9.84
14.54	67.14	97.06	1.30	99.52	ASA + Rivaroxaban 2.5mg	75.20	1.12
0.22	13.63	50.51	0.04	74.86	1.79	ASA + Prasugrel 10mg	0.00
0.00	17.41	68.16	0.01	90.64	1.70	35.40	ASA + Clopidogrel 75mg

Posterior probabilities (%) of hazard ratio < 0.8 for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 5.53% that the hazard ratio is below 0.8 (ie, there was a 5.53% probability for Rivaroxaban 5mg superiority).

eTable 11: Posterior Probabilities of Hazard Ratio > 1.25

ASA	0.00	0.00	0.00	0.00	0.00	0.00	0.03
76.79	Rivaroxaban 5mg	0.10	0.04	0.19	0.00	0.00	0.84
100.00	72.41	Ticagrelor 60mg	0.11	0.00	0.00	0.00	1.68
0.06	0.01	0.00	Clopidogrel 75mg	49.40	17.16	0.92	36.89
100.00	91.36	47.58	100.00	Ticagrelor 90mg	0.03	0.00	1.74
19.31	3.04	0.03	79.15	0.00	ASA + Rivaroxaban 2.5mg	0.11	15.01
87.69	41.61	6.88	98.60	2.02	79.42	ASA + Prasugrel 10mg	94.09
86.11	26.52	0.73	98.95	0.06	72.36	12.75	ASA + Clopidogrel 75mg

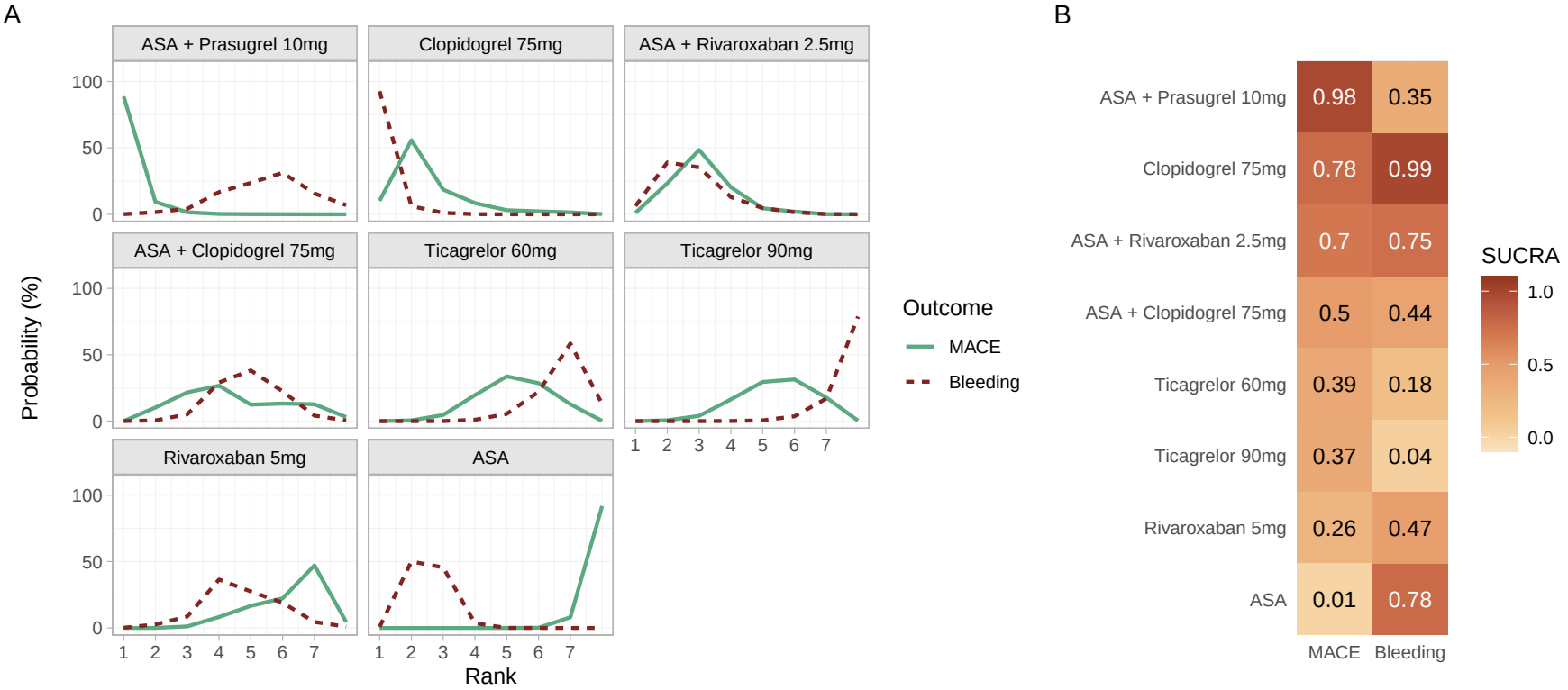
Posterior probabilities (%) of hazard ratio < 0.8 for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 0.00% that the hazard ratio is below 0.8 (ie, there was a 0.00% probability for Rivaroxaban 5mg superiority).

eTable 12: Posterior Probabilities of Hazard Ratio within the ROPE

ASA	94.47	83.95	11.18	85.76	13.95	0.50	52.02
22.94	Rivaroxaban 5mg	97.21	37.97	97.40	71.01	3.94	80.80
0.00	26.42	Ticagrelor 60mg	52.74	100.00	84.25	6.56	89.83
14.45	2.31	0.00	Clopidogrel 75mg	50.49	80.86	42.14	61.79
0.00	8.50	50.50	0.00	Ticagrelor 90mg	80.96	5.96	88.42
66.15	29.83	2.91	19.55	0.47	ASA + Rivaroxaban 2.5mg	24.69	83.86
12.09	44.76	42.61	1.36	23.11	18.79	ASA + Prasugrel 10mg	5.91
13.89	56.06	31.11	1.04	9.30	25.94	51.85	ASA + Clopidogrel 75mg

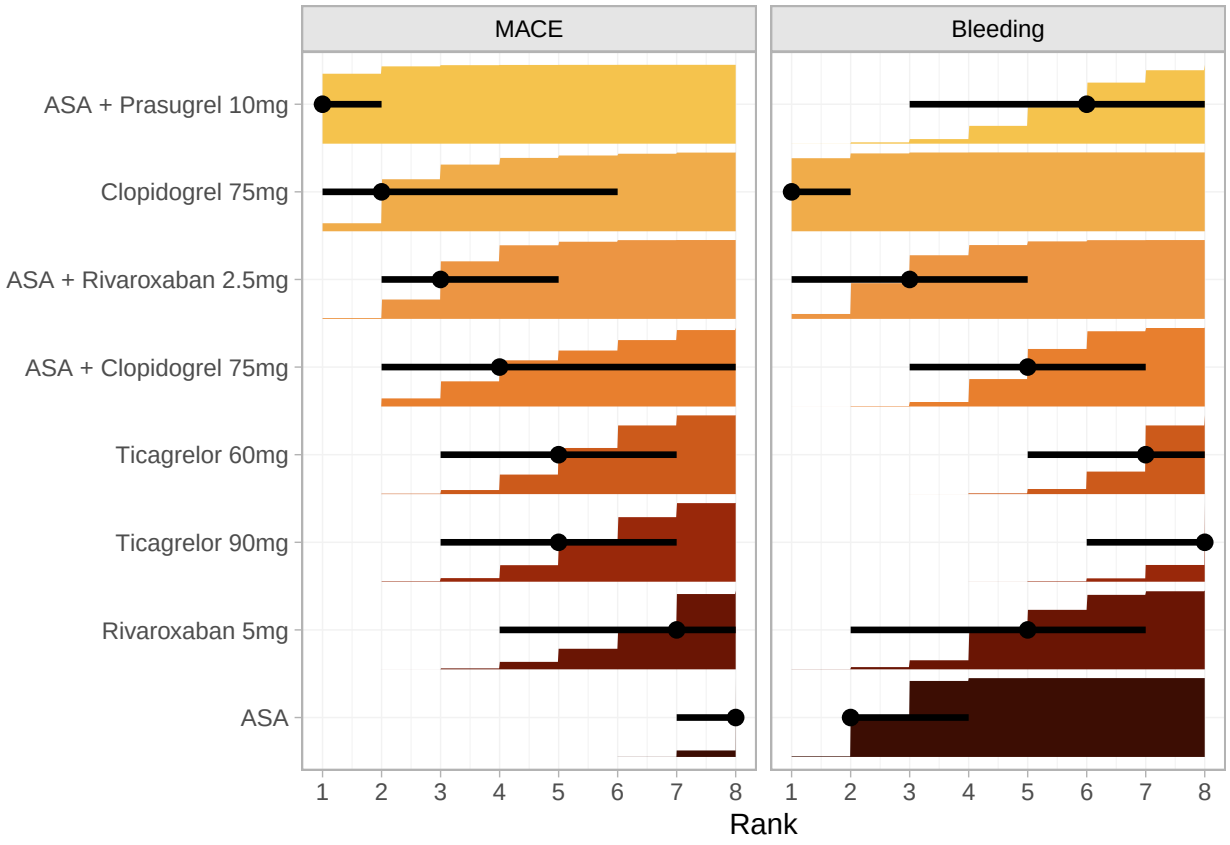
Posterior probabilities (%) of hazard ratio within the region of practical equivalence (ROPE), ie, between 0.80 and 1.25, for the MACE or Bleeding outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the MACE outcome. Results to the left (left lower half table) correspond to the Bleeding outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 94.47% that the hazard ratio is within the ROPE.

eFigure 5: Ranks and SUCRA



Panel A: Ranking probabilities for MACE (solid line) and Bleeding (dotted line) outcomes for each treatment. Panel B: Heatmap with corresponding SUCRA values. While each row corresponds to a treatment, each column depicts one outcome.

eFigure 6: Ranks with Uncertainty

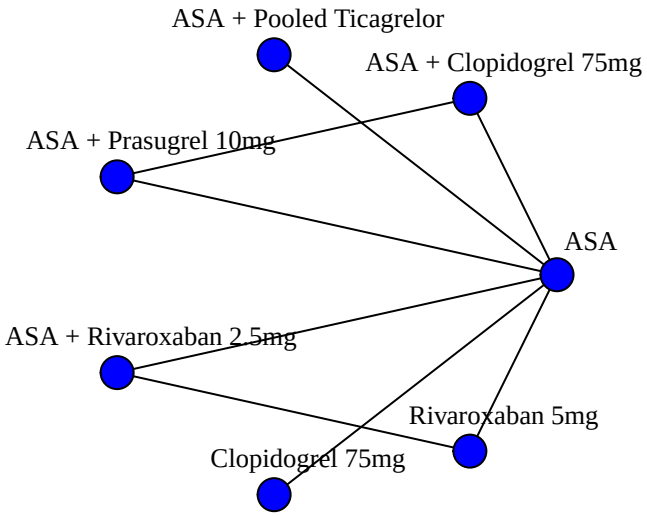


Marginal posterior distributions for the rank of each treatment. Left panel depicts ranks for MACE, while right panel for the Bleeding outcome. In each panel, there are a point estimate, interval bar, and bar plot for each treatment (Y-axis). The point estimate represents the median rank. The interval bar shows the 95% credible interval of the underlying marginal posterior distribution. Lastly, the bar plot shows the cumulative distribution function (CDF).

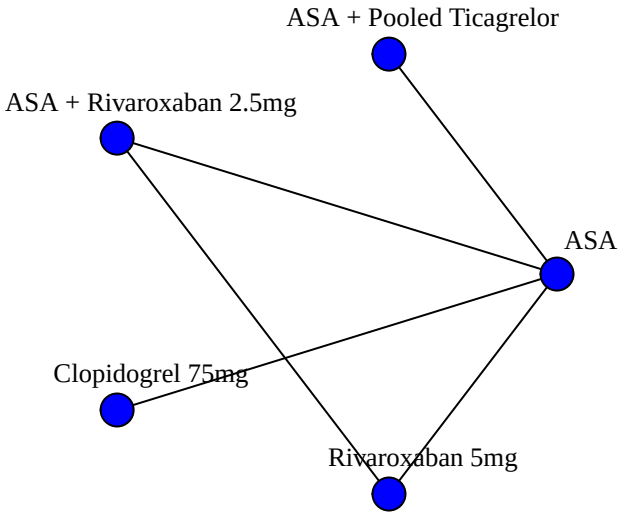
Pooled Ticagrelor Networks: Secondary Outcomes

eFigure 7: Network Plots

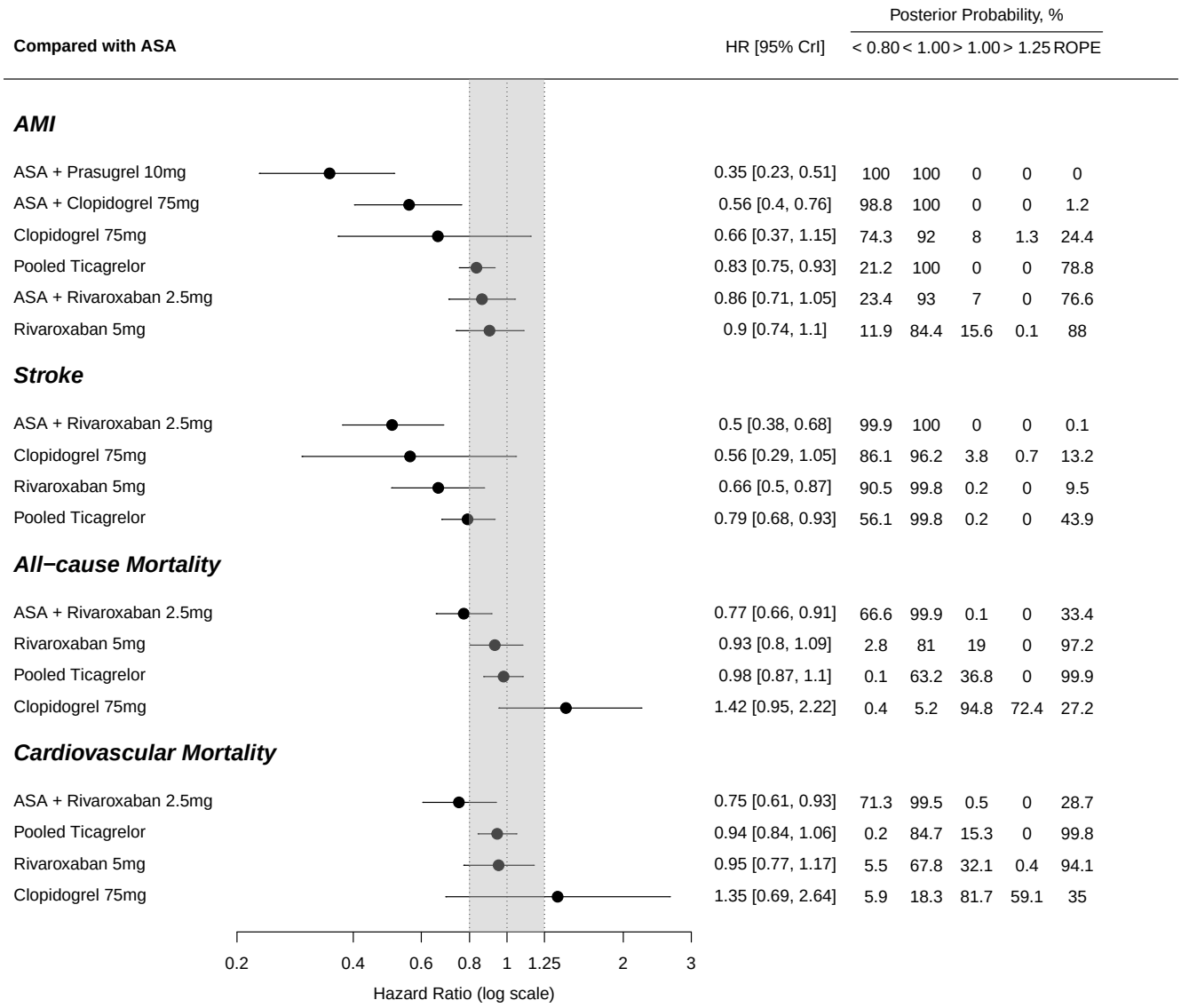
Acute Myocardial Infarction



Ischemic Stroke, All-cause Mortality, and Cardiovascular Mortality



eFigure 8: Forest Plot



Treatment effects compared to ASA on MACE and Bleeding outcomes, ordered according to underlying SUCRA values. HR below 1.0 favors the experimental treatment. On the left, treatment names are depicted. In the middle, forest plot shows each treatment effect median and 95% credible intervals. Gray area corresponds to the ROPE (from 0.8 to 1.25 HR). On the right, exact effect sizes along with posterior probabilities are shown.

Abbreviations: ROPE, region of practical equivalence; HR, hazard ratio.

League Tables

eTables 13-15: Median and 95% Credible Intervals

Acute Myocardial Infarction

ASA	0.90 (0.74, 1.10)	0.66 (0.37, 1.15)	0.86 (0.71, 1.05)	0.35 (0.23, 0.51)	0.56 (0.40, 0.76)	0.83 (0.75, 0.93)
	Rivaroxaban 5mg	0.73 (0.40, 1.35)	0.96 (0.79, 1.17)	0.38 (0.25, 0.60)	0.62 (0.43, 0.90)	0.93 (0.75, 1.16)
		Clopidogrel 75mg	1.30 (0.73, 2.44)	0.53 (0.26, 1.04)	0.84 (0.45, 1.65)	1.26 (0.71, 2.32)
			ASA + Rivaroxaban 2.5mg	0.40 (0.26, 0.64)	0.65 (0.44, 0.94)	0.97 (0.77, 1.20)
				ASA + Prasugrel 10mg	1.60 (1.13, 2.21)	2.40 (1.57, 3.59)
					ASA + Clopidogrel 75mg	1.49 (1.07, 2.10)
						Pooled Ticagrelor

Hazard ratios (95% credible interval) for the Acute Myocardial Infarction outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, the corresponding HR (95% CrI) was 0.90 (0.74, 1.10), favoring Rivaroxaban 5mg (ie, HR < 1.0).

Ischemic Stroke

ASA	0.66 (0.50, 0.87)	0.56 (0.29, 1.05)	0.50 (0.38, 0.68)	0.79 (0.68, 0.93)
	Rivaroxaban 5mg	0.84 (0.43, 1.67)	0.76 (0.56, 1.00)	1.19 (0.87, 1.63)
		Clopidogrel 75mg	0.90 (0.45, 1.80)	1.41 (0.73, 2.68)
			ASA + Rivaroxaban 2.5mg	1.57 (1.13, 2.20)
				Pooled Ticagrelor

Hazard ratios (95% credible interval) for the Ischemic Stroke outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, the corresponding HR (95% CrI) was 0.66 (0.50, 0.87), favoring Rivaroxaban 5mg (ie, HR < 1.0).

All-cause and Cardiovascular Mortality

ASA	0.93 (0.80, 1.09)	1.42 (0.95, 2.22)	0.77 (0.66, 0.91)	0.98 (0.87, 1.10)
0.95 (0.77, 1.17)	Rivaroxaban 5mg	1.52 (0.98, 2.41)	0.83 (0.71, 0.98)	1.05 (0.87, 1.28)
1.35 (0.69, 2.64)	1.42 (0.71, 2.82)	Clopidogrel 75mg	0.54 (0.35, 0.85)	0.69 (0.44, 1.07)
0.75 (0.61, 0.93)	0.79 (0.63, 0.97)	0.56 (0.28, 1.12)	ASA + Rivaroxaban 2.5mg	1.27 (1.03, 1.55)
0.94 (0.84, 1.06)	0.99 (0.79, 1.27)	0.70 (0.36, 1.37)	1.26 (0.97, 1.60)	Pooled Ticagrelor

Hazard ratios (95% credible interval) for the All-cause or Cardiovascular mortality outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the All-cause mortality outcome. Results to the left (left lower half table) correspond to the Cardiovascular mortality outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for All-cause mortality, the corresponding HR (95% CrI) was 0.93 (0.80, 1.09), favoring Rivaroxaban 5mg (ie, HR < 1.0).

eTables 16-18: Posterior Probabilities of Hazard Ratio < 1.0

Acute Myocardial Infarction

ASA	84.41	91.96	93.05	100.00	99.99	99.99
	Rivaroxaban 5mg	84.44	66.90	100.00	99.49	75.36
		Clopidogrel 75mg	19.30	96.45	69.55	21.73
			ASA + Rivaroxaban 2.5mg	100.00	98.88	60.91
				ASA + Prasugrel 10mg	0.34	0.00
					ASA + Clopidogrel 75mg	0.84
						Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 1.0 for the Acute Myocardial Infarction outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 84.41% that the hazard ratio is below 1.0 (ie, there was a 84.41% probability for Rivaroxaban 5mg superiority).

Ischemic Stroke

ASA	99.78	96.21	100.00	99.84
	Rivaroxaban 5mg	67.96	96.91	14.72
		Clopidogrel 75mg	61.85	15.14
			ASA + Rivaroxaban 2.5mg	0.47
				Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 1.0 for the Ischemic Stroke outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 99.78% that the hazard ratio is below 1.0 (ie, there was a 99.78% probability for Rivaroxaban 5mg superiority).

All-cause and Cardiovascular Mortality

ASA	81.00	5.22	99.88	63.21
67.85	Rivaroxaban 5mg	3.20	99.01	31.13
18.30	15.59	Clopidogrel 75mg	99.55	95.09
99.51	98.32	95.00	ASA + Rivaroxaban 2.5mg	1.09
84.67	52.39	85.71	3.71	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 1.0 for the All-cause or Cardiovascular mortality outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the All-cause mortality outcome. Results to the left (left lower half table) correspond to the Cardiovascular mortality outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for All-cause mortality, there was a posterior probability of 81.00% that the hazard ratio is below 1.0 (ie, there was a 81.00% probability for Rivaroxaban 5mg superiority).

eTables 19-21: Posterior Probabilities of Hazard Ratio < 0.8

Acute Myocardial Infarction

ASA	11.95	74.31	23.38	100.00	98.76	21.18
	Rivaroxaban 5mg	61.42	4.20	99.96	91.38	10.10
		Clopidogrel 75mg	5.47	87.78	43.68	6.42
			ASA + Rivaroxaban 2.5mg	99.92	86.95	4.42
				ASA + Prasugrel 10mg	0.01	0.00
					ASA + Clopidogrel 75mg	0.00
						Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 0.80 for the Acute Myocardial Infarction outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 11.95% that the hazard ratio is below 0.80.

Ischemic Stroke

ASA	90.46	86.09	99.90	56.12
	Rivaroxaban 5mg	44.45	63.78	0.69
		Clopidogrel 75mg	37.50	4.54
			ASA + Rivaroxaban 2.5mg	0.00
				Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 0.80 for the Ischemic Stroke outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. A hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 90.46% that the hazard ratio is below 0.80.

All-cause and Cardiovascular Mortality

ASA	2.84	0.35	66.61	0.09
5.51	Rivaroxaban 5mg	0.26	33.65	0.43
5.90	5.30	Clopidogrel 75mg	95.43	74.46
71.29	54.85	85.20	ASA + Rivaroxaban 2.5mg	0.00
0.24	4.01	65.56	0.00	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio < 0.80 for the All-cause or Cardiovascular mortality outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the All-cause mortality outcome. Results to the left (left lower half table) correspond to the Cardiovascular mortality outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for All-cause mortality, there was a posterior probability of 2.84% that the hazard ratio is below 0.80.

eTables 22-24: Posterior Probabilities of Hazard Ratio > 1.25

Acute Myocardial Infarction

ASA	0.06	1.32	0.00	0.00	0.00	0.00
	Rivaroxaban 5mg	4.19	0.35	0.00	0.01	0.41
		Clopidogrel 75mg	55.04	0.91	11.80	51.45
			ASA + Rivaroxaban 2.5mg	0.00	0.04	1.20
				ASA + Prasugrel 10mg	92.62	99.90
					ASA + Clopidogrel 75mg	85.66
						Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio > 1.25 for the Acute Myocardial Infarction outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 0.06% that the hazard ratio is above 1.25.

Ischemic Stroke

ASA	0.00	0.66	0.00	0.00
	Rivaroxaban 5mg	13.48	0.00	38.48
		Clopidogrel 75mg	18.57	64.20
			ASA + Rivaroxaban 2.5mg	90.22
				Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio > 1.25 for the Ischemic Stroke outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 0.00% that the hazard ratio is above 1.25.

All-cause and Cardiovascular Mortality

ASA	0.00	72.41	0.00	0.00
0.41	Rivaroxaban 5mg	80.41	0.00	3.99
59.11	64.08	Clopidogrel 75mg	0.00	0.41
0.00	0.00	1.29	ASA + Rivaroxaban 2.5mg	56.09
0.00	3.02	4.54	51.69	Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio > 1.25 for the All-cause or Cardiovascular mortality outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the All-cause mortality outcome. Results to the left (left lower half table) correspond to the Cardiovascular mortality outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for MACE, there was a posterior probability of 0.00% that the hazard ratio is above 1.25.

eTables 25-27: Posterior Probabilities of Hazard Ratio within the ROPE

Acute Myocardial Infarction

ASA	87.99	24.36	76.62	0.00	1.24	78.83
	Rivaroxaban 5mg	34.39	95.45	0.04	8.61	89.49
		Clopidogrel 75mg	39.49	11.31	44.52	42.12
			ASA + Rivaroxaban 2.5mg	0.07	13.01	94.38
				ASA + Prasugrel 10mg	7.36	0.10
					ASA + Clopidogrel 75mg	14.34
						Pooled Ticagrelor

Posterior probabilities (%) of hazard ratio within the region of practical equivalence (ROPE), ie, between 0.80 and 1.25, for the Acute Myocardial Infarction outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 87.99% that the hazard ratio is within the ROPE.

Ischemic Stroke

ASA	9.54	13.25	0.10	43.88
	Rivaroxaban 5mg	42.08	36.23	60.84
		Clopidogrel 75mg	43.92	31.26
			ASA + Rivaroxaban 2.5mg	9.78
				Pooled Ticagrelor

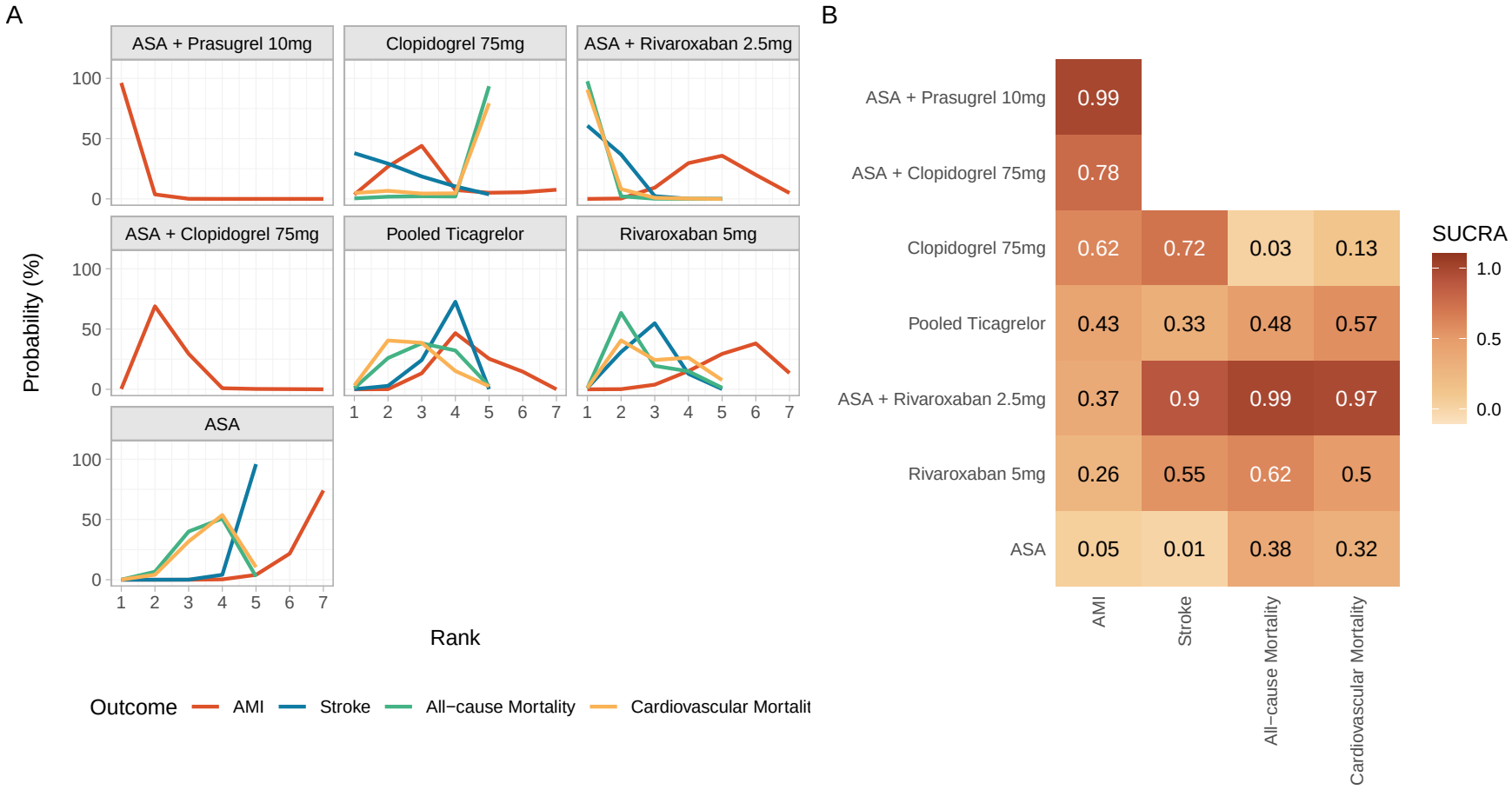
Posterior probabilities (%) of hazard ratio within the region of practical equivalence (ROPE), ie, between 0.80 and 1.25, for the Ischemic Stroke outcome. Treatments are shown in the diagonal. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison, there was a posterior probability of 9.54% that the hazard ratio is within the ROPE.

All-cause and Cardiovascular Mortality

ASA	97.16	27.24	33.39	99.91
67.85	Rivaroxaban 5mg	19.32	66.35	95.59
18.30	15.59	Clopidogrel 75mg	4.58	25.12
99.51	98.32	95.00	ASA + Rivaroxaban 2.5mg	43.91
84.67	52.39	85.71	3.71	Pooled Ticagrelor

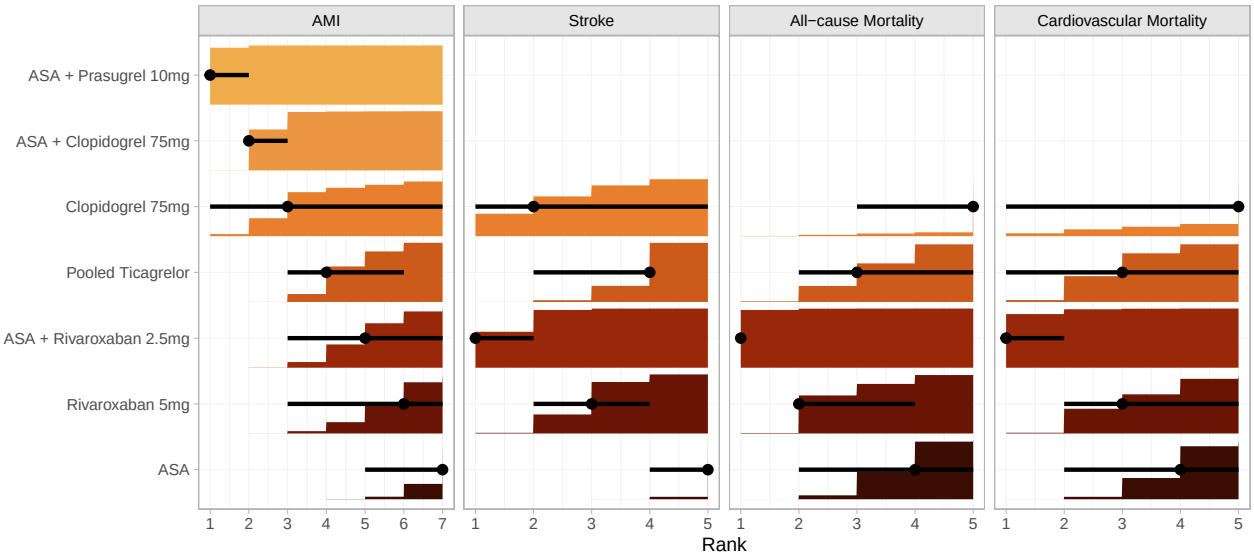
Posterior probabilities (%) of hazard ratio within the region of practical equivalence (ROPE), ie, between 0.80 and 1.25, for the All-cause or Cardiovascular mortality outcomes. Treatments are shown in the diagonal. Results to the right of this diagonal (right upper half table) correspond to the All-cause mortality outcome. Results to the left (left lower half table) correspond to the Cardiovascular mortality outcome. Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For both outcomes, a hazard ratio < 1.0 favors the column-defining treatment. For example, in the Rivaroxaban 5mg vs. ASA comparison for All-cause mortality, there was a posterior probability of 97.16% that the hazard ratio is within the ROPE.

eFigure 9: Ranks + SUCRA



Panel A: Ranking probabilities for Acute Myocardical Infarction (AMI), Stroke, All-cause and Cardiovascular Mortality outcomes for each treatment. There are only AMI rankings for "ASA + Prasugrel 10mg" and "ASA + Clopidogrel 75mg" because there was no data available for other outcomes in corresponding studies. Panel B: Heatmap with corresponding SUCRA values. While each row corresponds to a treatment, each column depicts one outcome.

eFigure 10: Ranks with Uncertainty



Marginal posterior distributions for the rank of each treatment. Each panel corresponds to a separate outcome, labeled on top. In each panel, there are a point estimate, interval bar, and bar plot for each treatment (Y-axis). The point estimate represents the median rank. The interval bar shows the 95% credible (quantile) interval of the underlying marginal posterior distribution. Lastly, the bar plot shows the cumulative distribution function (CDF).

CINeMA

eTables 28-33: Pooled Ticagrelor Networks

MACE

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low

Bleeding

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Prasugrel 10mg	Some concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Clopidogrel 75mg	Some concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. ASA + Prasugrel 10mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. ASA + Clopidogrel 75mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Prasugrel 10mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low

Acute Myocardial Infarction

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Prasugrel 10mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low

Ischemic Stroke

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low

All-cause Mortality

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low

Cardiovascular Mortality

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low

eTables 34-35: Separate Dosages Ticagrelor Networks

MACE

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. ASA + Prasugrel 10mg	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. ASA + Clopidogrel 75mg	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low

Bleeding

Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall rating
ASA vs. Rivaroxaban 5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. Clopidogrel 75mg	No concerns	Undetected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. Clopidogrel 75mg	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
Rivaroxaban 5mg vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Prasugrel 10mg	Some concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. ASA + Clopidogrel 75mg	Some concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
Rivaroxaban 5mg vs. Pooled Ticagrelor	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Rivaroxaban 2.5mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
Clopidogrel 75mg vs. ASA + Prasugrel 10mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	No concerns	Not applicable	Major concerns	Low
Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Rivaroxaban 2.5mg vs. ASA + Prasugrel 10mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. ASA + Clopidogrel 75mg	Some concerns	Suspected	No concerns	Some concerns	Not applicable	Major concerns	Very Low
ASA + Rivaroxaban 2.5mg vs. Pooled Ticagrelor	Some concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low
ASA + Prasugrel 10mg vs. ASA + Clopidogrel 75mg	No concerns	Undetected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Prasugrel 10mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	Major concerns	Not applicable	Major concerns	Very Low
ASA + Clopidogrel 75mg vs. Pooled Ticagrelor	No concerns	Suspected	No concerns	No concerns	Not applicable	Major concerns	Low