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Supplementary Material 1: Search strategy.

SEARCH SYNTAX and SEARCH STRING (in PubMed) for RCTs

1. Clopidogrel
2. Ticagrelor
3. Prasugrel
4. P2y12 inhibitor
5. ADP receptor antagonist
6. 1 OR 2 OR 3 OR 4 OR 5
7. acute coronary syndrome
8. acute myocardial infarction
9. st elevation myocardial infarction
10. non-st elevation myocardial infarction
11. non-st elevation acute coronary syndrome
12. unstable angina
13. 7 OR 8 OR 9 OR 10 OR 11 OR 12
14. Precision-sensitivity maximizing RCT search filter from Cochrane
15. 6 AND 13 AND 14

((((((clopidogrel) OR (ticagrelor)) OR (prasugrel)) OR (p2y12 inhibitor)) OR (adp receptor antagonist)) AND ((((((acute coronary syndrome) OR (acute myocardial infarction)) OR (st elevation myocardial infarction)) OR (non-st elevation myocardial infarction)) OR (non-st elevation acute coronary syndrome)) OR (unstable angina))) AND (((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))) (((((("clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields]) OR "clopidogrel s"[All Fields]) OR ("ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields])) OR (((("prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields])) OR "prasugrel hydrochloride"[All Fields]) OR "prasugrel"[All Fields]) OR "prasugrel s"[All Fields])) OR ("p2y12"[All Fields] AND (((("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "inhibitors"[All Fields]) OR "inhibitor"[All Fields]) OR "inhibitor s"[All Fields]))) OR (((("receptors, purinergic p2"[MeSH Terms] OR ("receptors"[All Fields] AND "purinergic"[All Fields]) AND "p2"[All Fields]) OR "purinergic p2 receptors"[All Fields]) OR ("adp"[All Fields] AND "receptor"[All Fields]) OR "adp receptor"[All Fields]) AND (((("antagonist"[All Fields] OR "antagonists and inhibitors"[MeSH Subheading]) OR ("antagonists"[All Fields] AND "inhibitors"[All Fields])) OR "antagonists and inhibitors"[All Fields]) OR "antagonists"[All Fields])) AND ((((((("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields]) AND "syndrome"[All Fields])) OR "acute coronary syndrome"[All Fields]) OR (((("acute"[All Fields] OR "acutely"[All Fields]) OR "acutes"[All Fields]) AND ((("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields])) OR "myocardial infarction"[All Fields]))) OR ((("st elevation myocardial infarction"[MeSH Terms] OR (((("st"[All Fields] AND "elevation"[All Fields]) AND "myocardial"[All Fields]) AND "infarction"[All Fields])) OR "st elevation myocardial infarction"[All Fields])) OR (((("non-st elevated myocardial infarction"[MeSH Terms] OR (((("non-st"[All Fields] AND "elevated"[All Fields]) AND "myocardial"[All Fields]) AND "infarction"[All Fields])) OR "non st

elevated myocardial infarction"[All Fields]) OR (((("non"[All Fields] AND "st"[All Fields]) AND "elevation"[All Fields]) AND "myocardial"[All Fields]) AND "infarction"[All Fields]) OR "non st elevation myocardial infarction"[All Fields]) OR ("non-st"[All Fields] AND (((("elevate"[All Fields] OR "elevated"[All Fields]) OR "elevates"[All Fields]) OR "elevating"[All Fields]) OR "elevation"[All Fields]) OR "elevational"[All Fields]) OR "elevations"[All Fields]) AND (("acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields]) AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields])) OR (((("angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields]) OR ("unstable"[All Fields] AND "angina"[All Fields]))) AND (((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type]) OR "randomized"[Title/Abstract]) OR "placebo"[Title/Abstract]) OR "clinical trials as topic"[MeSH Terms:noexp]) OR "randomly"[Title/Abstract]) OR "trial"[Title]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]))

Translations

clopidogrel: "clopidogrel"[MeSH Terms] OR "clopidogrel"[All Fields] OR "clopidogrel's"[All Fields]

ticagrelor: "ticagrelor"[MeSH Terms] OR "ticagrelor"[All Fields] OR "ticagrelor's"[All Fields]

prasugrel: "prasugrel hydrochloride"[MeSH Terms] OR ("prasugrel"[All Fields] AND "hydrochloride"[All Fields]) OR "prasugrel hydrochloride"[All Fields] OR "prasugrel"[All Fields] OR "prasugrel's"[All Fields]

inhibitor: "antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor's"[All Fields]

adp receptor: "receptors, purinergic p2"[MeSH Terms] OR ("receptors"[All Fields] AND "purinergic"[All Fields] AND "p2"[All Fields]) OR "purinergic p2 receptors"[All Fields] OR ("adp"[All Fields] AND "receptor"[All Fields]) OR "adp receptor"[All Fields]

antagonist: "antagonist"[All Fields] OR "antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "antagonists"[All Fields]

acute coronary syndrome: "acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]

acute: "acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]

myocardial infarction: "myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]

st elevation myocardial infarction: "st elevation myocardial infarction"[MeSH Terms] OR ("st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "st elevation myocardial infarction"[All Fields]

non-st elevation myocardial infarction: "non-st elevated myocardial infarction"[MeSH Terms] OR ("non-st"[All Fields] AND "elevated"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non-st elevated myocardial infarction"[All Fields] OR ("non"[All Fields] AND "st"[All Fields] AND "elevation"[All Fields] AND "myocardial"[All Fields] AND "infarction"[All Fields]) OR "non st elevation myocardial infarction"[All Fields]

elevation: "elevate"[All Fields] OR "elevated"[All Fields] OR "elevates"[All Fields] OR "elevating"[All Fields] OR "elevation"[All Fields] OR "elevational"[All Fields] OR "elevations"[All Fields]

acute coronary syndrome: "acute coronary syndrome"[MeSH Terms] OR ("acute"[All Fields] AND "coronary"[All Fields] AND "syndrome"[All Fields]) OR "acute coronary syndrome"[All Fields]

unstable angina: "angina, unstable"[MeSH Terms] OR ("angina"[All Fields] AND "unstable"[All Fields]) OR "unstable angina"[All Fields] OR ("unstable"[All Fields] AND "angina"[All Fields])

clinical trials as topic[mesh:noexp]: "clinical trials as topic"[MeSH Terms:noexp]

animals[mh]: "animals"[MeSH Terms]

humans [mh]: "humans"[MeSH Terms]

Supplementary Material 2: Table with Characteristics of eligible trials

STUDY AND YEAR OF PUBLICATION	POPULATION	N OF PATIENTS WITH NSTE-ACS (% OF TOTAL)	INVASIVE MANAGEMENT (% OF TOTAL)	TREATMENT ARMS	EFFICACY OUTCOME	MAJOR BLEEDING DEFINITION	FOLLOW-UP DURATION (MEDIAN)
WIVIOT ET AL. 2007 (TRITON-TIMI 38)	ACS with scheduled PCI	10074 (74%)	99.1%	1. Prasugrel (n = 6813) 2. Clopidogrel (n = 6795)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	TIMI major bleeding not related to CABG	14.5 months
WALLENTIN ET AL. 2009 (PLATO)	Hospitalized for ACS, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours	11080 (59.5%)	51.6%	1. Ticagrelor (n = 9333) 2. Clopidogrel (n = 9291)	Composite of death from vascular causes, myocardial infarction, or stroke.	PLATO major bleeding	9.2 months
ROE ET AL. 2012 (TRILOGY-ACS)	ACS patients selected for a final treatment strategy of medical management without revascularization within 10 days after the index event	9326 (100%)	0%	1. Prasugrel (n = 4663) 2. Clopidogrel (n = 4663)	Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	TIMI major bleeding not related to CABG	17 months
SAITO ET AL. 2014 (PRASFIT-ACS)	Japanese ACS patients	680 (49.1%)	100%	1. Prasugrel reduced dose (n = 685) 2. Clopidogrel (n = 678)	Composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke.	TIMI major bleeding not related to CABG	12 months

STUDY AND YEAR OF PUBLICATION	POPULATION	N OF PATIENTS WITH NSTEMI-ACS (% OF TOTAL)	INVASIVE MANAGEMENT (% OF TOTAL)	TREATMENT ARMS	EFFICACY OUTCOME	MAJOR BLEEDING DEFINITION	FOLLOW-UP DURATION (MEDIAN)
GOTO ET AL. 2015 (PHILO)	Japanese, Korean and Taiwanese ACS patients	368 (45.9%)	86.1%	1. Ticagrelor (n = 401) 2. Clopidogrel (n = 400)	Time to first occurrence of MI, stroke or death from vascular causes	PLATO major bleeding	7 months
MOTOVSKA ET AL. 2017 (PRAGUE-18)	Patients with AMI treated with a primary PCI strategy	72 (5.9%)	99.2%	1. Prasugrel (n = 634) 2. Ticagrelor (n = 596)	Occurrence of cardiovascular death, non-fatal MI, or stroke	Not provided	12 months
PARK ET AL. 2019 (TICAKOREA)	Korean ACS with or without ST elevation	474 (59.3%)	85.6%	1. Ticagrelor (n = 400) 2. Clopidogrel (n = 400)	Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke	PLATO major bleeding	12 months
SCHÜPKE ET AL. 2019 (ISAR-REACT 5)	ACS patients	2365 (58.9%)	79.9%	1. Ticagrelor (n = 2012) 2. Prasugrel (n = 2006)	Composite of death, myocardial infarction, or stroke	BARC type 3 to 5	12 months
GIMBEL ET AL. 2020 (POPULAR AGE)	Patients aged 70 years or older with NSTEMI-ACS	1002 (100%)	63.8%	1. Clopidogrel (n = 500) 2. Ticagrelor or prasugrel (n = 502)	First primary outcome: any bleeding requiring medical intervention, defined as PLATO major or minor bleeding. Second primary outcome: net clinical benefit of all-cause death, myocardial infarction, stroke and PLATO major or minor bleeding	PLATO major bleeding	12 months

Supplementary Material 3: Quality assessment of included studies.



Supplementary Material 4: Assessment of inconsistency, funnel plot and impact of individual studies for the primary efficacy outcome.

Table C.1. Node-splitting method for assessment of inconsistency in network meta-analysis.

Comparison	k	prop	NMA	Direct	Indirect	RoR	z	p-value
Clopidogrel : Prasugrel	4	0.86	1.23	1.20	1.44	0.83	-0.64	0.52
Clopidogrel : Ticagrelor	3	0.74	0.99	1.04	0.86	1.20	0.64	0.52
Prasugrel : Ticagrelor	2	0.40	0.80	0.72	0.86	0.83	-0.64	0.52

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

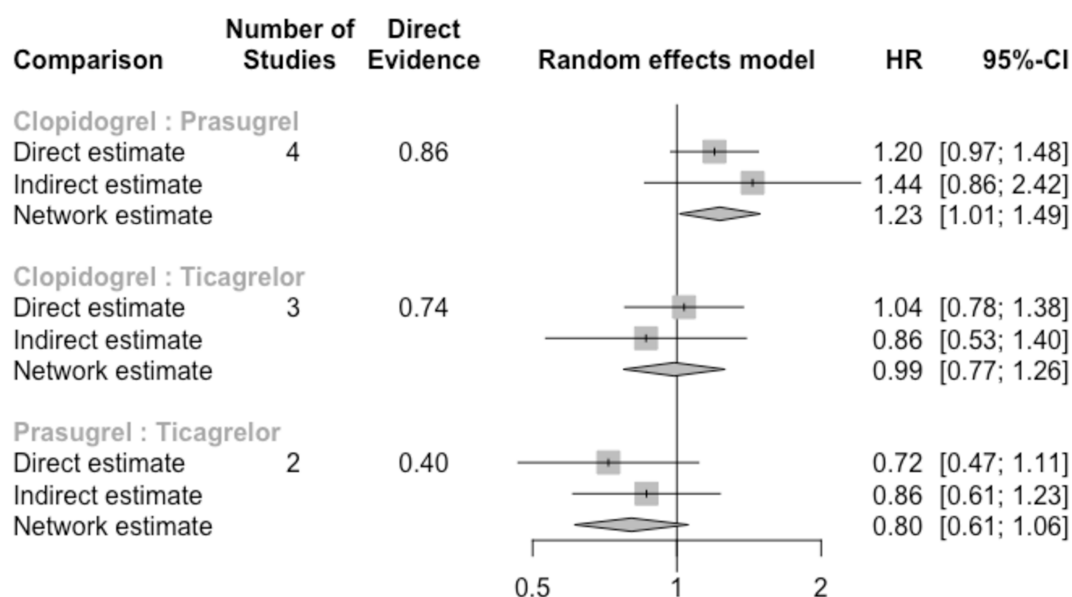


Figure C.1. Forest plot of the direct and indirect evidence for the individual comparisons.

Table C.2. Node-splitting method for assessment of inconsistency in network meta-analysis after excluding patients with conservative management.

Comparison	k	prop	NMA	Direct	Indirect	RoR	z	p-value
Clopidogrel : Prasugrel	3	0.81	1.32	1.31	1.37	0.96	-0.16	0.88
Clopidogrel : Ticagrelor	3	0.72	0.97	0.99	0.94	1.05	0.16	0.88
Prasugrel : Ticagrelor	2	0.48	0.74	0.72	0.76	0.96	-0.16	0.88

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

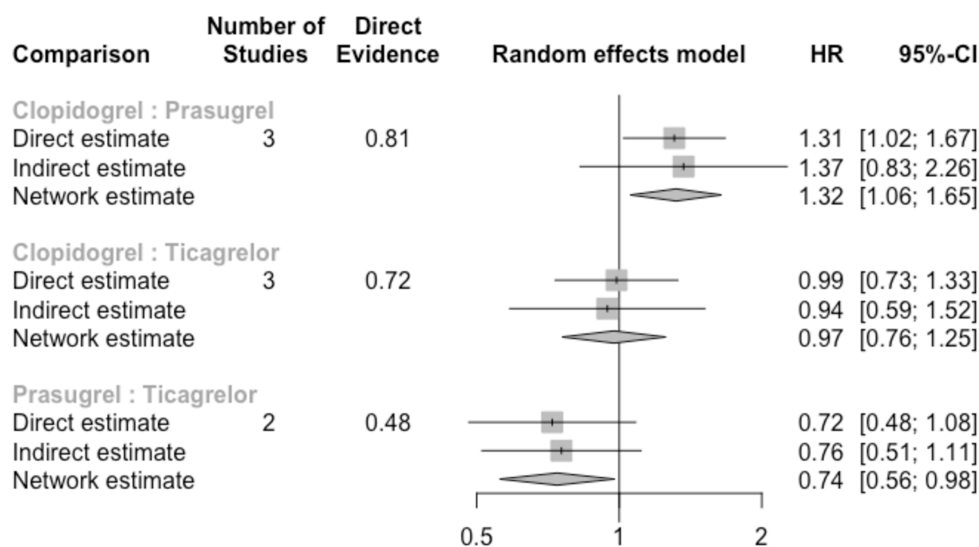


Figure C.2. Forest plot of the direct and indirect evidence for the individual comparisons after excluding patients with conservative management.

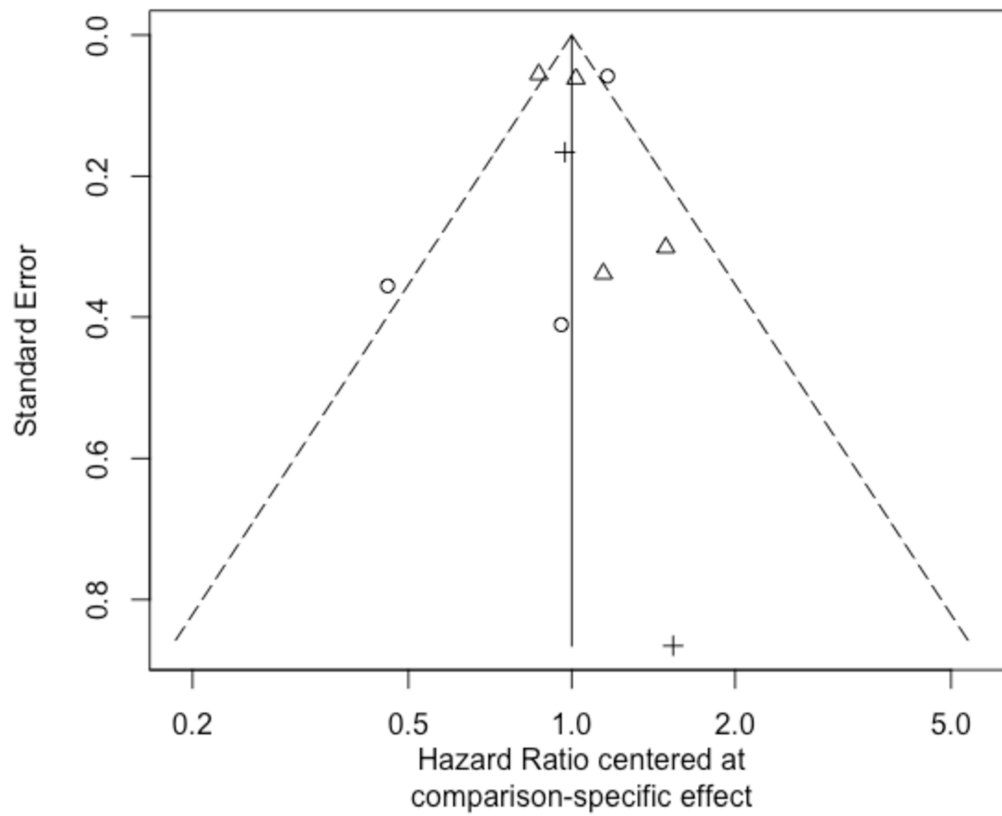


Figure C.3. Funnel plot of studies contributing in the network for the primary outcome.

Table C.3. Impact of individual studies in the network meta-analysis for the primary efficacy outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.35	0.03	0.12
Wallentin 2009	0.07	0.56	0.39
Roe 2012	0.36	0.03	0.12
Saito 2014_UA	0.07	0.004	0.02
Saito 2014_NSTEMI	0.09	0.005	0.02
Goto 2015	0.005	0.08	0.04
Motovska 2017	0.006	0.01	0.03

Park 2019	0.007	0.10	0.06
Schüpke 2019	0.13	0.24	0.37

Supplementary Material 5: Network meta-analysis of interventions for the cardiovascular death outcome.

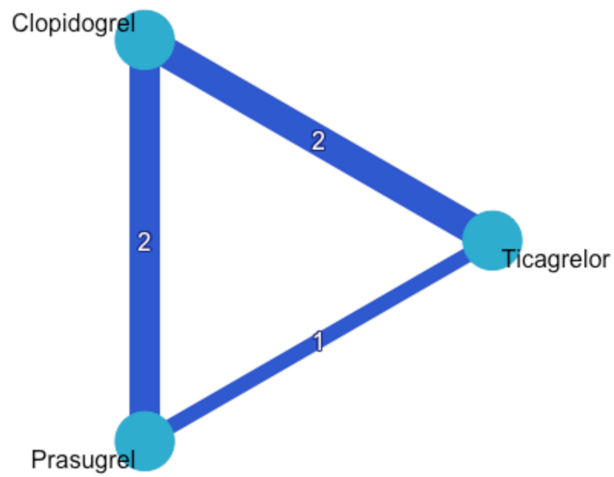


Figure D.1. Network graph of interventions for the cardiovascular death outcome.

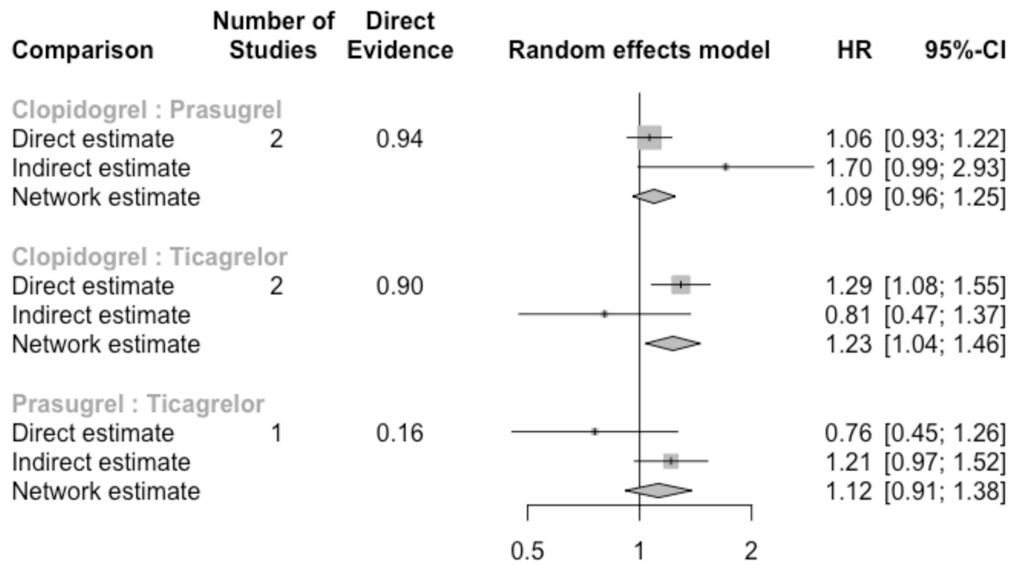


Figure D.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the cardiovascular death outcome.

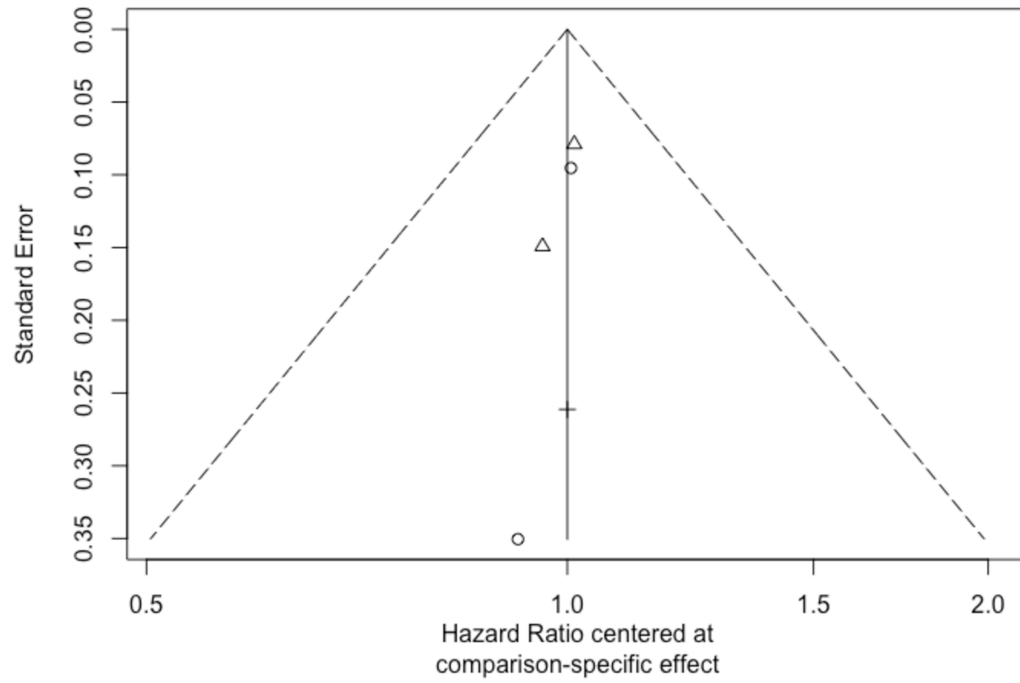


Figure D.3. Funnel plot of studies contributing in the network for the cardiovascular death outcome.

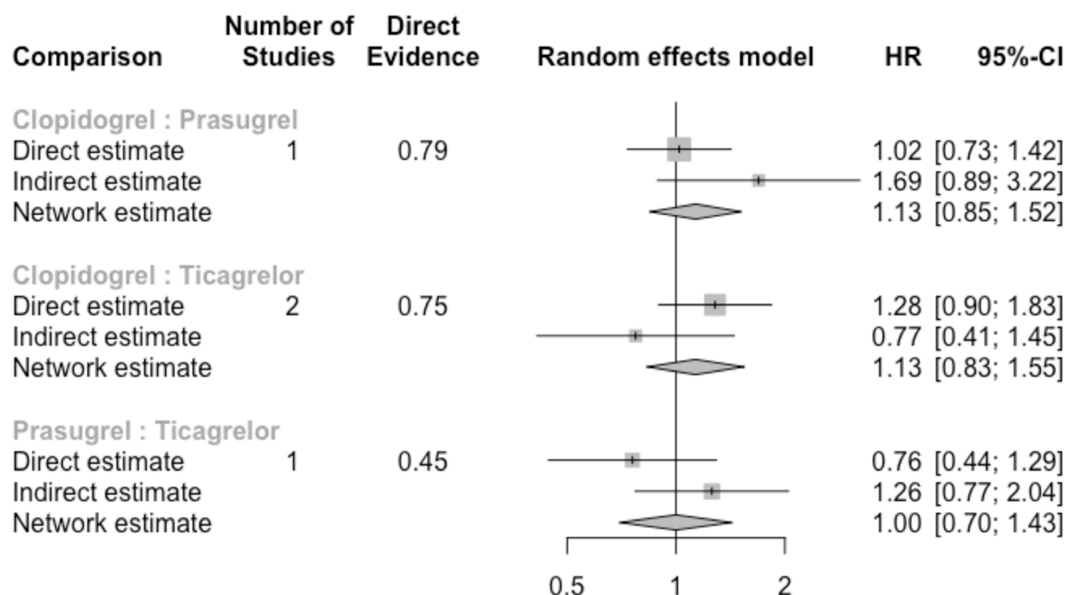


Figure D.4. . Forest plot of the network estimates of the potent P2Y12 inhibitors for the cardiovascular death outcome in the sensitivity analysis.

Table D.1. Impact of individual studies in the network meta-analysis for the cardiovascular death outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.21	0.01	0.08
Wallentin 2009	0.04	0.83	0.75
Roe 2012	0.73	0.02	0.47
Schüpke 2019	0.06	0.10	0.16
Gimbel 2020	0.01	0.06	0.04

Supplementary Material 6: Network meta-analysis of interventions for the all-cause mortality outcome.

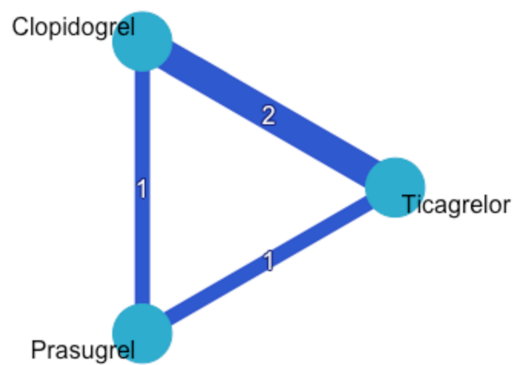


Figure E.1. Network graph of interventions for the all-cause death outcome.

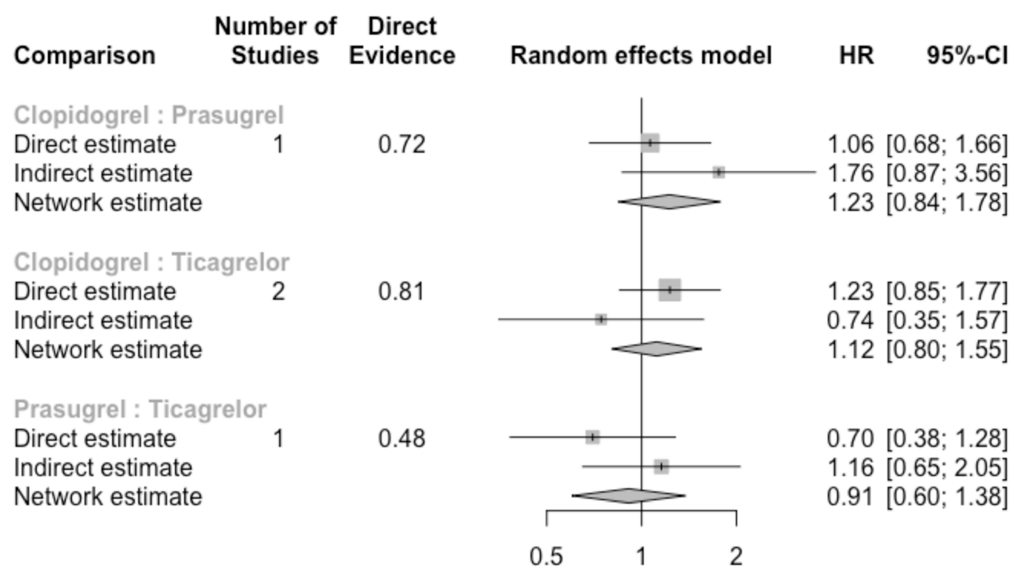


Figure E.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the all-cause mortality outcome.

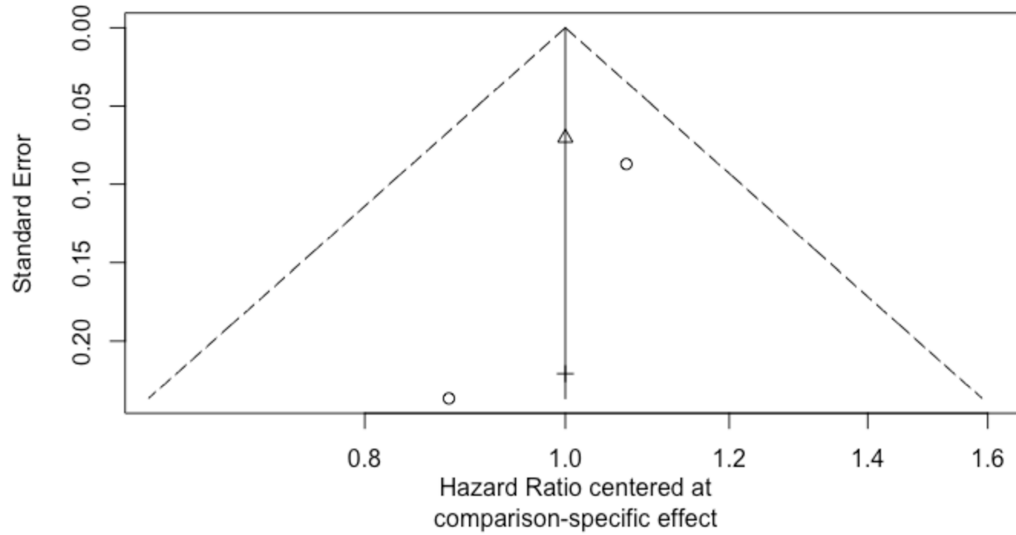


Figure E.3. Funnel plot of studies contributing in the network for the all-cause death outcome.

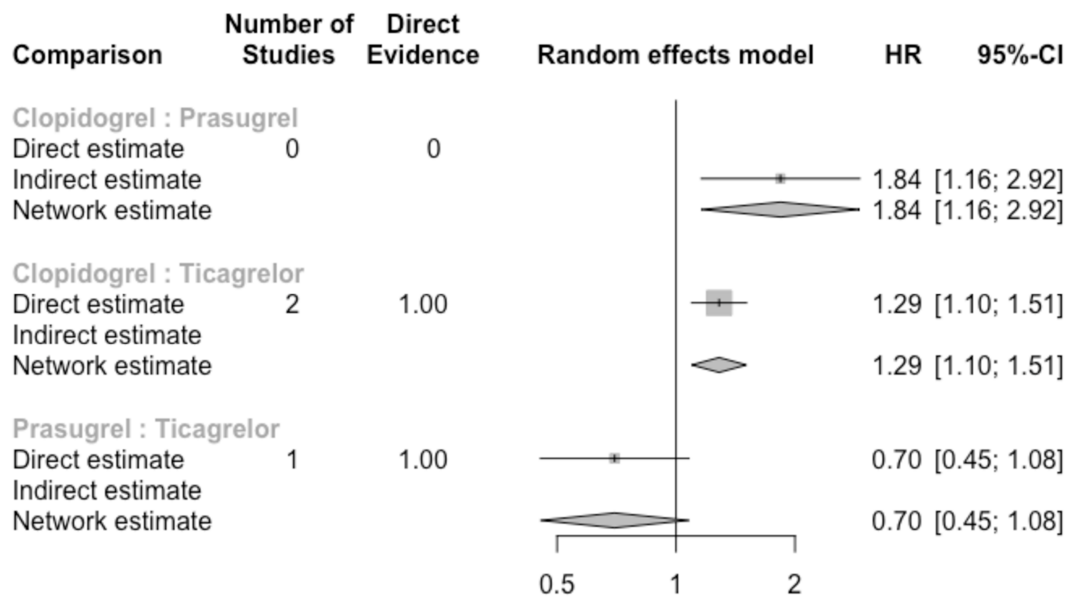


Figure E.4. . Forest plot of the network estimates of the potent P2Y12 inhibitors for the all-cause death outcome in the sensitivity analysis.

Table E.1. Impact of individual studies in the network meta-analysis for the all-cause death outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wallentin 2009	0.10	0.53	0.23
Roe 2012	0.72	0.19	0.52
Schüpke 2019	0.28	0.19	0.48
Gimbel 2020	0.04	0.28	0.09

Supplementary Material 7: Network meta-analysis of interventions for the myocardial infarction outcome.

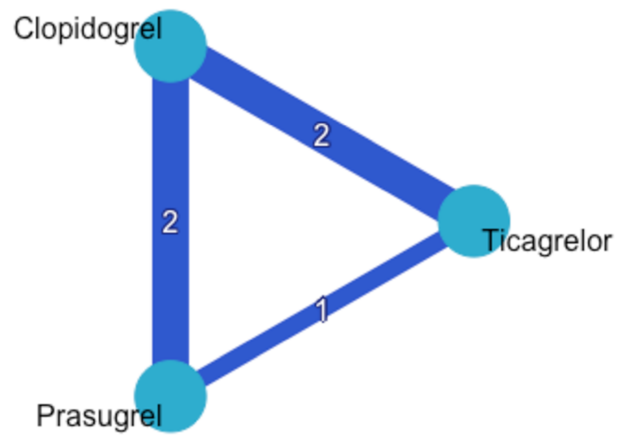


Figure F.1. Network graph of interventions for the myocardial infarction outcome.

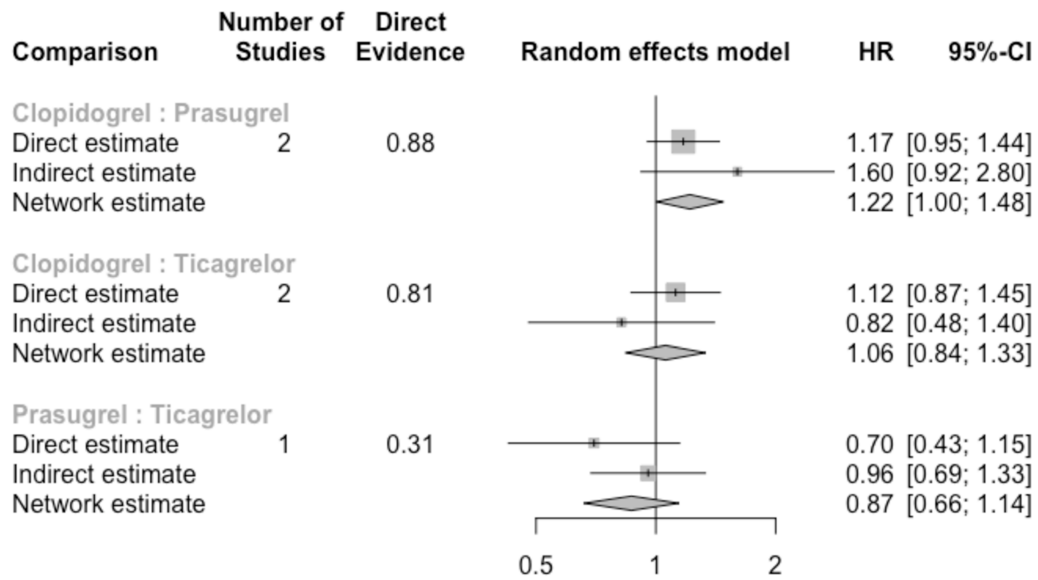


Figure F.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the myocardial infarction outcome.

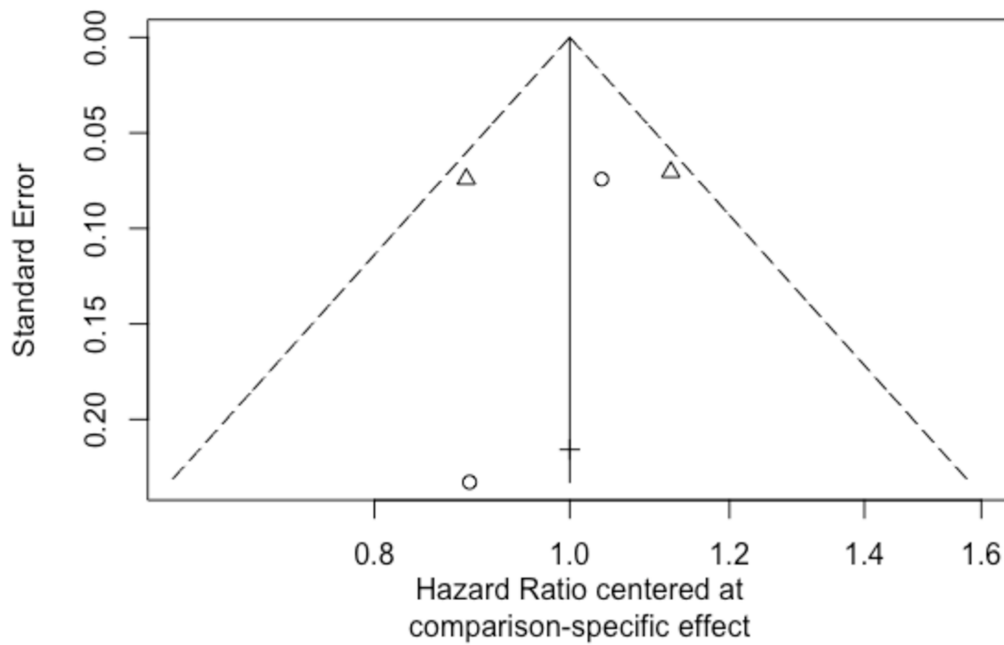


Figure F.3. Funnel plot of studies contributing in the network for the myocardial infarction outcome.

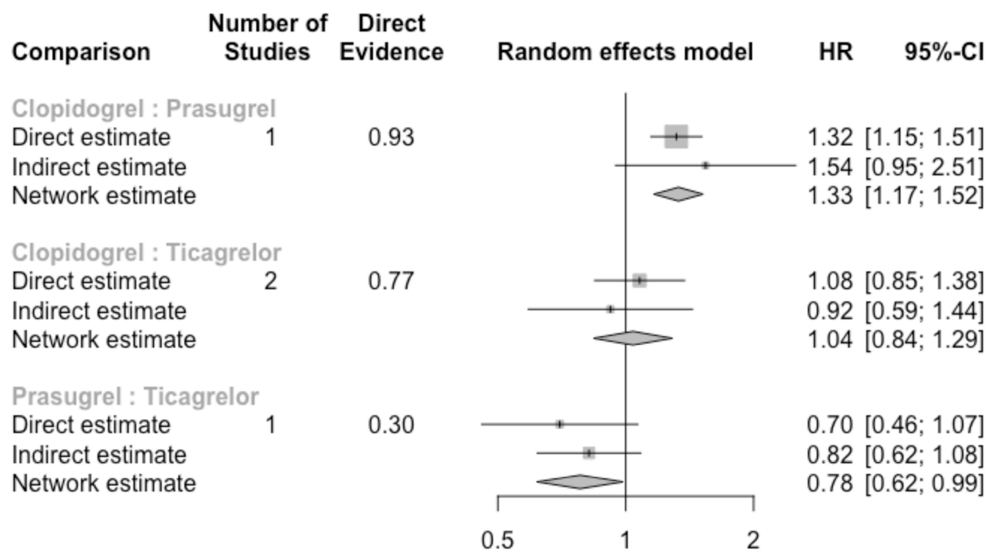


Figure F.4. . Forest plot of the network estimates of the potent P2Y12 inhibitors for the myocardial infarction outcome in the sensitivity analysis.

Table F.1. Impact of individual studies in the network meta-analysis for the myocardial infarction outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.44	0.02	0.20
Wallentin 2009	0.05	0.62	0.45
Roe 2012	0.43	0.02	0.19
Schüpke 2019	0.12	0.19	0.31
Gimbel 2020	0.01	0.20	0.11

Supplementary Material 8: Network meta-analysis of interventions for the stroke outcome.

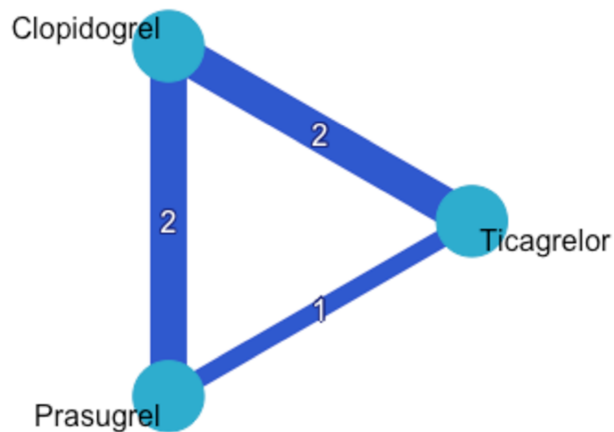


Figure G.1. Network graph of interventions for the stroke outcome.

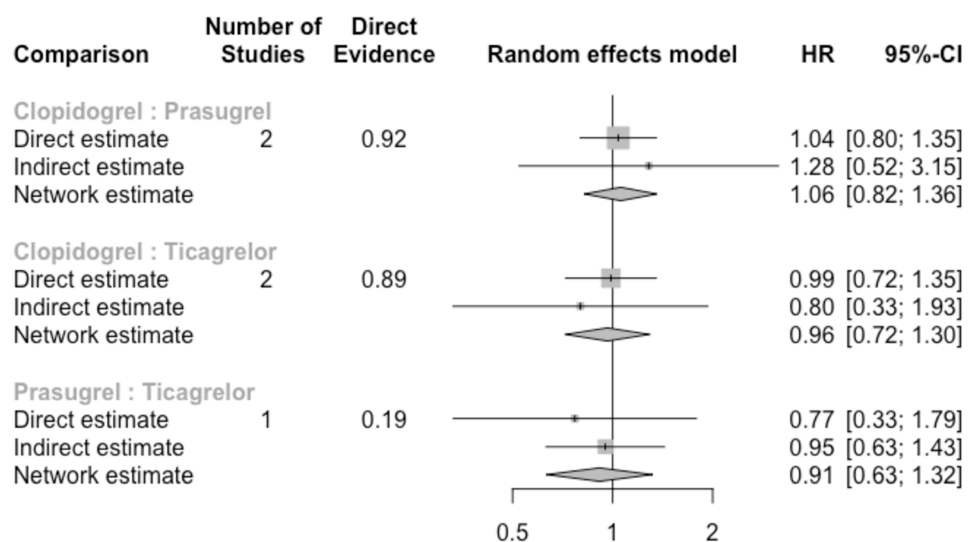


Figure G.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the stroke outcome.

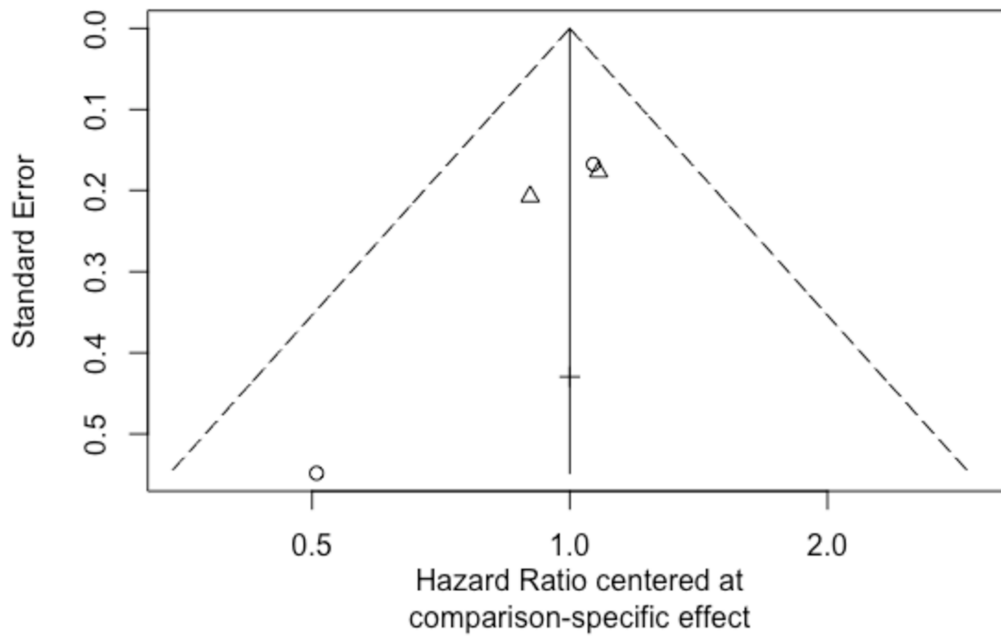


Figure G.3. Funnel plot of studies contributing in the network for the stroke outcome.

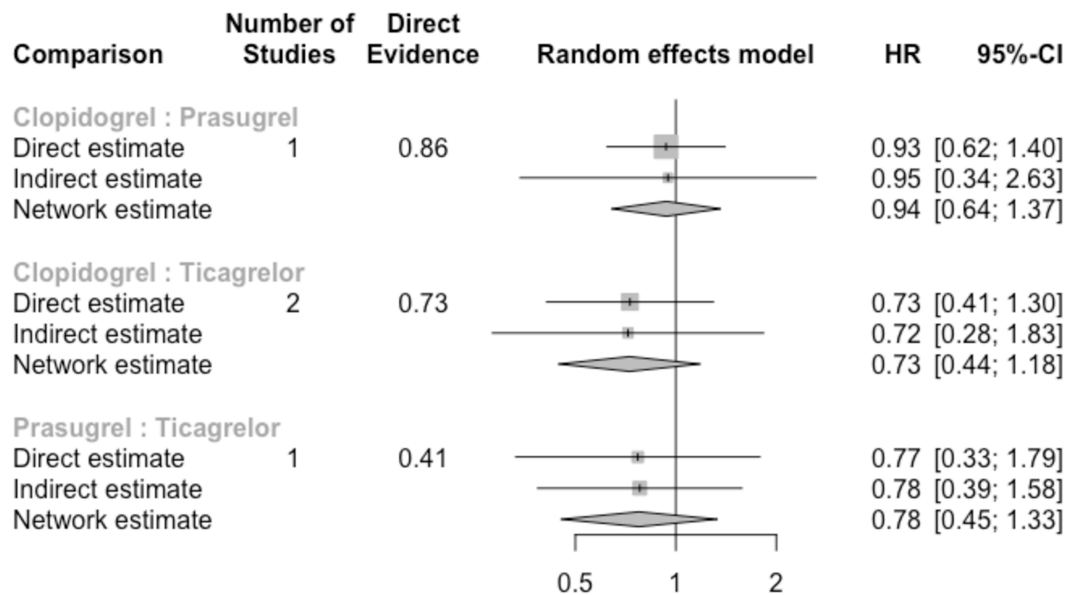


Figure G.4. . Forest plot of the network estimates of the potent P2Y12 inhibitors for the stroke outcome in the sensitivity analysis.

Table G.1. Impact of individual studies in the network meta-analysis for the myocardial infarction outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.39	0.01	0.19
Wallentin 2009	0.05	0.81	0.70
Roe 2012	0.53	0.01	0.29
Schüpke 2019	0.08	0.11	0.19
Gimbel 2020	0.01	0.08	0.04

Supplementary Material 9: Network meta-analysis of interventions for the stent thrombosis outcome.

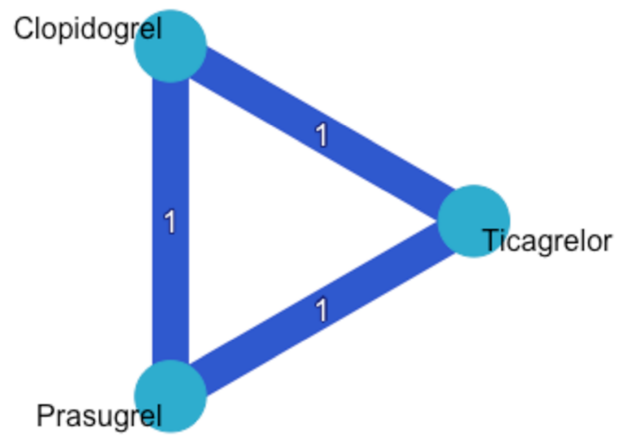


Figure H.1. Network graph of interventions for the stent thrombosis outcome.

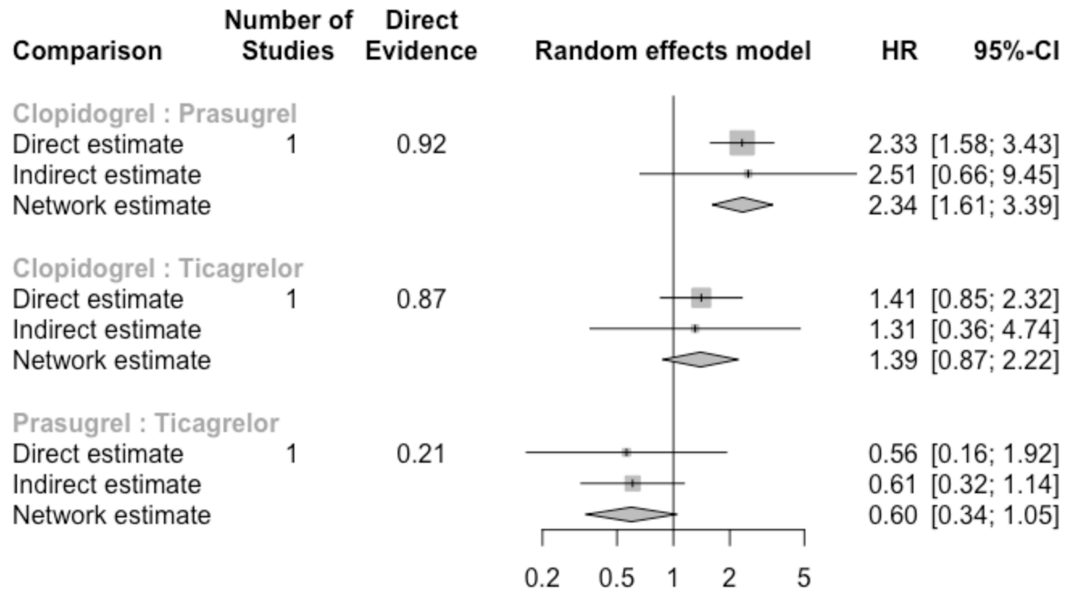


Figure H.2. Forest plot of the network estimates of the potent P2Y12 inhibitors for the stent thrombosis outcome.

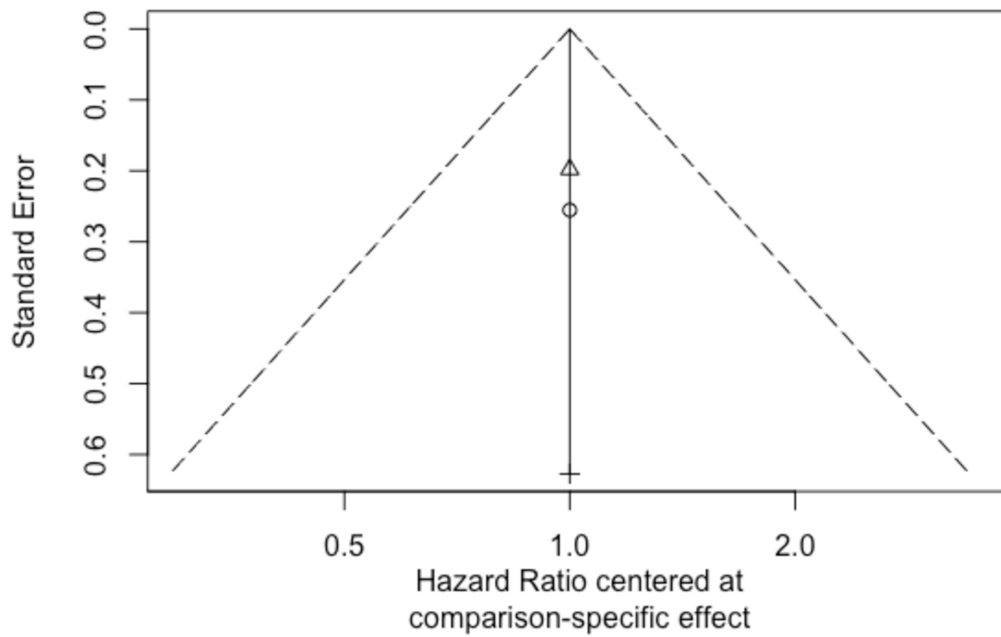


Figure H.3. Funnel plot of studies contributing in the network for the stent thrombosis outcome.

Table H.1. Impact of individual studies in the network meta-analysis for the stent thrombosis outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.92	0.13	0.79
Wallentin 2009	0.08	0.87	0.79
Schüpke 2019	0.08	0.13	0.21

Supplementary Material 10: Network meta-analysis of interventions for the safety outcomes.

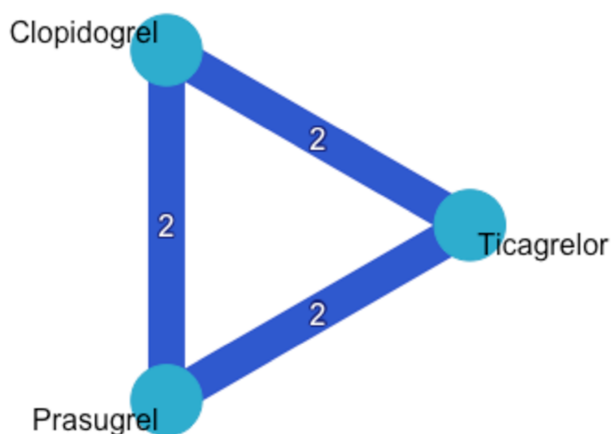


Figure 1.1. Network graph of interventions for the major bleeding safety outcome.

Table 1.1. Node-splitting method for assessment of inconsistency in network meta-analysis for the major bleeding outcome

Comparison	k	prop	NMA	Direct	Indirect	RoR	z	p-value
Clopidogrel : Prasugrel	2	0.75	0.87	0.76	1.32	0.58	-1.11	0.27
Clopidogrel : Ticagrelor	2	0.77	0.73	0.83	0.48	1.73	1.11	0.27
Prasugrel : Ticagrelor	2	0.49	0.84	0.63	1.10	0.58	-1.11	0.27

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

Table 1.2. Impact of individual studies in the network meta-analysis for the major bleeding outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.40	0.06	0.19
Wallentin 2009	0.08	0.45	0.21
Roe 2012	0.35	0.05	0.16
Motovska 2017	0.02	0.02	0.05
Schüpke 2019	0.22	0.21	0.44
Gimbel 2020	0.05	0.32	0.13

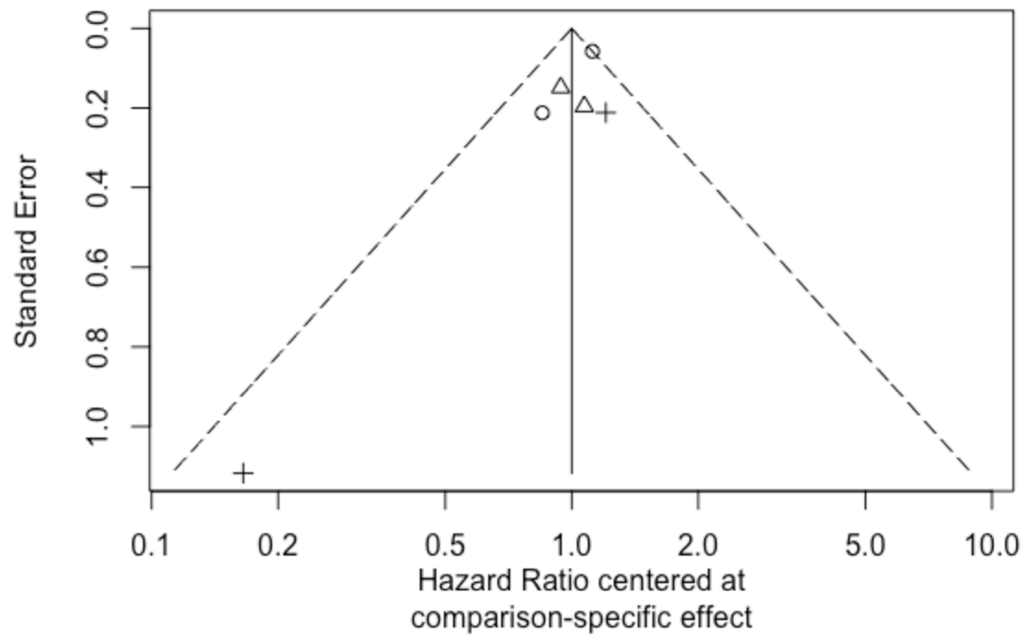


Figure 1.2. Funnel plot of studies contributing in the network for the major bleeding outcome.

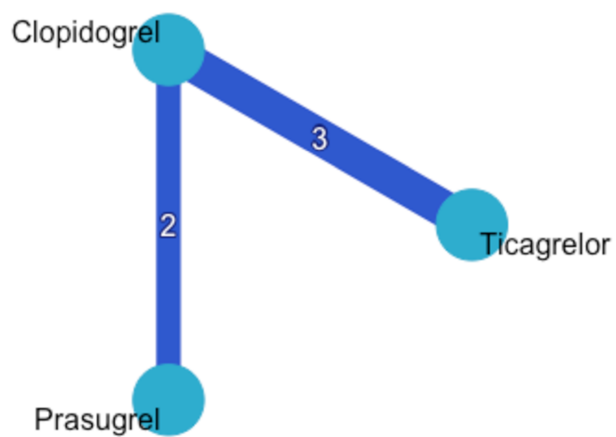


Figure 1.3. Network graph of interventions for the major or minor bleeding safety outcome.

Table I.3. Node-splitting method for assessment of inconsistency in network meta-analysis for the major or minor bleeding outcome

Comparison	k	Prop	NMA	Direct	Indirect	RoR	z	p-value
Clopidogrel : Prasugrel	2	1	0.73	0.73	-	-	-	-
Clopidogrel : Ticagrelor	3	1	0.78	0.78	-	-	-	-
Prasugrel : Ticagrelor	0	0	1.07	-	1.07	-	-	-

*k: Number of studies providing direct evidence, prop: Direct evidence proportion, NMA: Estimated treatment effect (HR) in network meta-analysis, Direct: Estimated treatment effect (HR) derived from direct evidence, Indirect: Estimated treatment effect (HR) derived from indirect evidence, RoR: Ratio of ratios (direct versus indirect), z: z-value of test for disagreement (direct versus indirect), p-value: p-value of test for disagreement (direct versus indirect).

Table I.4. Impact of individual studies in the network meta-analysis for the major or minor bleeding outcome.

Study	Clopidogrel : Prasugrel	Clopidogrel : Ticagrelor	Prasugrel : Ticagrelor
Wiviott 2007	0.60	0.00	0.46
Wallentin 2009	0.00	0.61	0.39
Roe 2012	0.40	0.00	0.29
Park 2019	0.00	0.08	0.04
Gimbel 2020	0.00	0.31	0.16

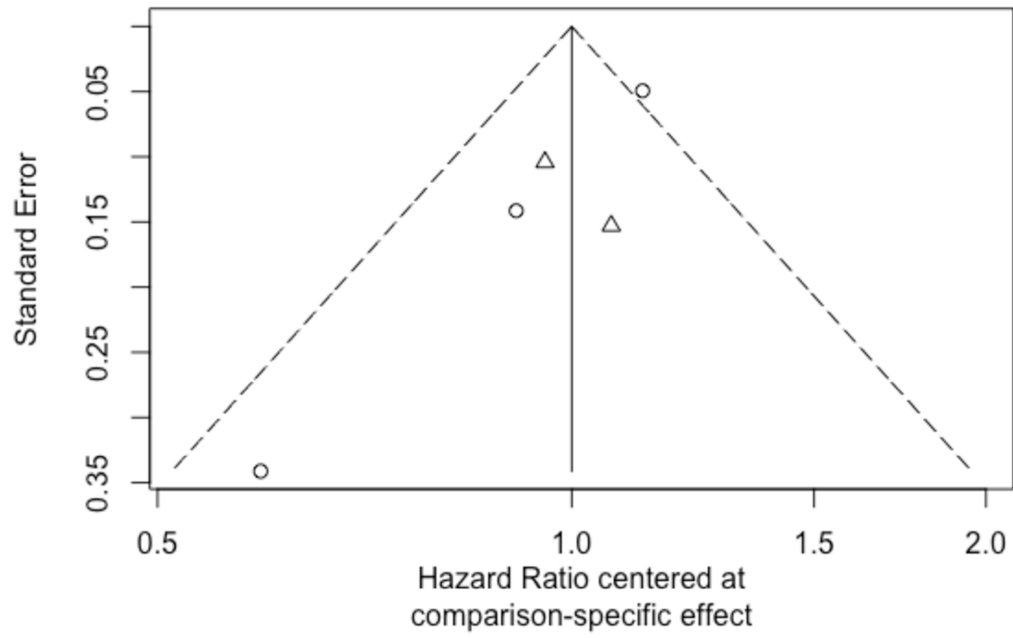
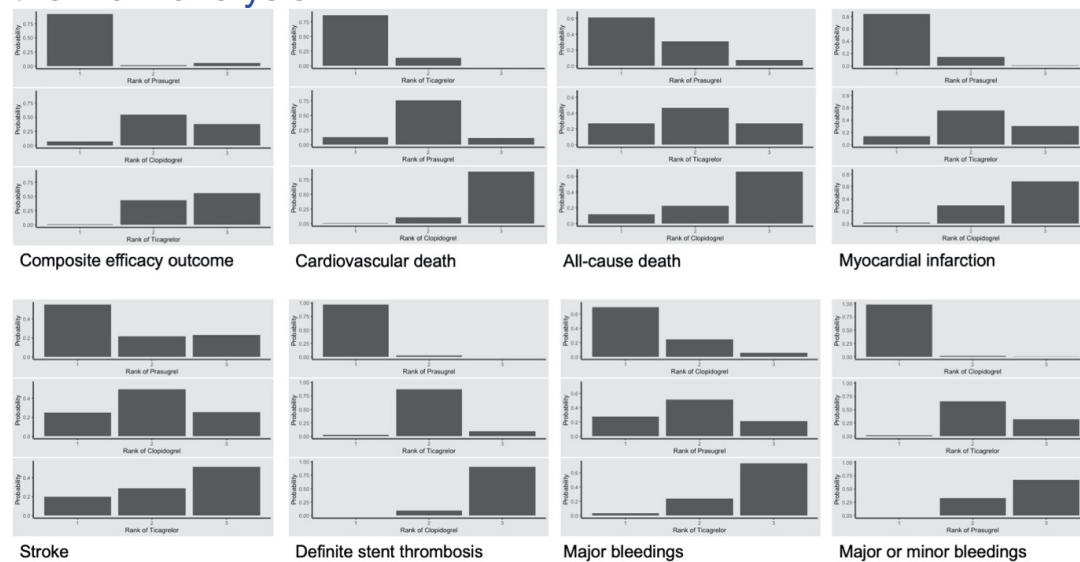


Figure I.4. Funnel plot of studies contributing in the network for the major or minor bleeding outcome.

Supplementary Material 11: Rankogram for every outcome in the main analysis.



Supplementary Material 12: Grading of evidence.

Table K.1. Grading of evidence in the network meta-analysis of P2Y12 inhibitors for the efficacy outcomes in the main analysis.

Pairwise comparison	Network meta-analysis estimate	Confidence	Downgrading due to
Composite efficacy outcome			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.23 (1.01;1.49)	Low	Heterogeneity
Clopidogrel : Ticagrelor	0.99 (0.78;1.27)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.80 (0.61;1.06)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Moderate	Inconsistency
Cardiovascular death			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.09 (0.96;1.25)	Low	Heterogeneity Incoherence
Clopidogrel : Ticagrelor	1.22 (1.04;1.46)	Low	Heterogeneity Incoherence
Prasugrel : Ticagrelor	1.12 (0.91;1.38)	Very low	Imprecision Heterogeneity Incoherence
<i>Ranking of treatments</i>		High	-
All-cause death			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.23 (0.84;1.78)	Low	Imprecision Heterogeneity
Clopidogrel : Ticagrelor	1.12 (0.80;1.55)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.91 (0.60;1.38)	Low	Imprecision
<i>Ranking of treatments</i>		Low	Imprecision Inconsistency
Myocardial infarction			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.22 (1.01;1.49)	Low	Heterogeneity
Clopidogrel : Ticagrelor	1.06 (0.84;1.33)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.87 (0.66;1.14)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Moderate	Inconsistency
Stroke			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.06 (0.82;1.36)	Low	Heterogeneity

Clopidogrel : Ticagrelor	0.97 (0.72;1.30)	Low	Heterogeneity
Prasugrel : Ticagrelor	0.91 (0.63;1.32)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Moderate	Imprecision
Definite stent thrombosis			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	2.34 (1.61;3.40)	Low	Heterogeneity
Clopidogrel : Ticagrelor	1.40 (0.86;2.22)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.60 (0.34;1.04)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		High	-

Imprecision: Confidence intervals include values favoring either treatment.

Incoherence: Disagreement between direct and indirect estimates.

Heterogeneity: Substantial between-study variance within the comparison.

Inconsistency: Evidence of heterogeneity in the network.

Table K.2. Grading of evidence in the network meta-analysis of P2Y12 inhibitors for the safety outcomes in the main analysis.

Pairwise comparison	Network meta-analysis estimate	Confidence	Downgrading due to
Major bleedings			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	0.87 (0.57;1.33)	Low	Imprecision Heterogeneity
Clopidogrel : Ticagrelor	0.73 (0.49;1.11)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.84 (0.52;1.38)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Very low	Imprecision Indirectness Inconsistency
Major or minor bleedings			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	0.73 (0.57;0.94)	Very low	Heterogeneity Incoherence
Clopidogrel : Ticagrelor	0.78 (0.63;0.96)	Very low	Within-study bias Heterogeneity Incoherence
<i>Indirect evidence. Hazard Ratio (95% Confidence Interval)</i>			
Prasugrel : Ticagrelor	1.07 (0.77;1.47)	Very low	Heterogeneity Incoherence
<i>Ranking of treatments</i>		Moderate	Indirectness

Imprecision: Confidence intervals include values favoring either treatment.

Incoherence: Disagreement between direct and indirect estimates.

Within-study bias: Dominated by evidence at high or moderate risk of bias.

Heterogeneity: Substantial between-study variance within the comparison.

Indirectness: Absence of agreement in outcome definition.

Inconsistency: Evidence of heterogeneity in the network.

Table K3. Grading of evidence in the network meta-analysis of P2Y₁₂ inhibitors for the outcomes in patients managed invasively (sensitivity analysis).

Pairwise comparison	Network meta-analysis estimate	Confidence	Downgrading due to
Composite efficacy outcome			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.32 (1.05;1.64)	Moderate	Heterogeneity
Clopidogrel : Ticagrelor	0.97 (0.76;1.25)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.74 (0.56;0.98)	Moderate	Heterogeneity
<i>Ranking of treatments</i>		High	-
Cardiovascular death			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.13 (0.84;1.52)	Low	Imprecision Heterogeneity
Clopidogrel : Ticagrelor	1.13 (0.83;1.55)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	1.00 (0.70;1.43)	Low	Imprecision
<i>Ranking of treatments</i>		Moderate	Imprecision
All-cause death			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.83 (1.16;2.91)	Very low	Heterogeneity Incoherence
Clopidogrel : Ticagrelor	1.29 (1.10;1.51)	Very low	Imprecision Heterogeneity Incoherence
Prasugrel : Ticagrelor	0.70 (0.45;1.08)	Very low	Heterogeneity Incoherence
<i>Ranking of treatments</i>		High	-
Myocardial infarction			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	1.33 (1.17;1.52)	Low	Heterogeneity
Clopidogrel : Ticagrelor	1.04 (0.84;1.29)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.78 (0.62;0.99)	Low	Heterogeneity
<i>Ranking of treatments</i>		High	-
Stroke			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	0.94 (0.64;1.37)	Low	Imprecision Heterogeneity

Pairwise comparison	Network meta-analysis estimate	Confidence	Downgrading due to
Clopidogrel : Ticagrelor	0.73 (0.45;1.19)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.78 (0.45;1.33)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Moderate	Imprecision
Definite stent thrombosis			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	2.34 (1.61;3.40)	Low	Heterogeneity
Clopidogrel : Ticagrelor	1.40 (0.86;2.22)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.60 (0.34;1.04)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		High	-
Major bleedings			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	0.89 (0.50;1.59)	Low	Imprecision
Clopidogrel : Ticagrelor	0.72 (0.45;1.18)	Low	Imprecision Heterogeneity
Prasugrel : Ticagrelor	0.82 (0.45;1.47)	Low	Imprecision Heterogeneity
<i>Ranking of treatments</i>		Very low	Imprecision Indirectness Inconsistency
Major or minor bleedings			
<i>Mixed evidence. Hazard Ratio (95% Confidence Interval)</i>			
Clopidogrel : Prasugrel	0.70 (0.53;0.93)	Very low	Heterogeneity Incoherence
Clopidogrel : Ticagrelor	0.73 (0.59;0.91)	Very low	Within-study bias Heterogeneity Incoherence
<i>Indirect evidence. Hazard Ratio (95% Confidence Interval)</i>			
Prasugrel : Ticagrelor	1.05 (0.73;1.50)	Very low	Heterogeneity Incoherence
<i>Ranking of treatments</i>		Moderate	Indirectness

Imprecision: Confidence intervals include values favoring either treatment.

Incoherence: Disagreement between direct and indirect estimates.

Within-study bias: Dominated by evidence at high or moderate risk of bias.

Heterogeneity: Substantial between-study variance within the comparison.

Indirectness: Absence of agreement in outcome definition.

Inconsistency: Evidence of heterogeneity in the network.

Supplementary Material 13: Hazard ratios of all outcomes across studies included in the systematic review

Study	Composite CV efficacy	CV death	All-cause death	MI	Stroke	Definite stent thrombosis	Major bleeding	Major or minor bleeding
TRITON-TIMI 38	0.82 (0.73;0.93)	0.98 (0.73;1.31)	-	0.76 (0.66;0.87)	1.07 (0.71;1.6)	0.43 (0.29;0.63)	1.4 (1.05;1.88)	1.43 (1.17;1.76)
PLATO*	0.83 (0.74;0.93)	0.77 (0.64;0.93)	0.76 (0.64;0.9)	0.86 (0.74;0.99)	0.95 (0.69;1.33)	0.71 (0.43;1.17)	1.07 (0.95;1.19)	1.14 (1.03;1.25)
TRILOGY-ACS**	0.96 (0.86;1.07)	0.93 (0.8;1.09)	0.94 (0.82;1.08)	0.96 (0.83;1.11)	0.89 (0.63;1.26)	-	1.23 (0.84;1.81)	1.28 (0.95;1.73)
PRASFIIT-ACS (UA)	0.73 (0.38;1.43)	-	-	-	-	-	-	-
PRASFIIT-ACS (NSTEMI)	0.56 (0.31;1.01)	-	-	-	-	-	-	-
PHILO	1.01 (0.45;2.25)	-	-	-	-	-	-	-
PRAGUE-18	0.47 (0.09;2.56)	-	-	-	-	-	3.84 (0.43;34.39)	-
TICAGO	2.11 (1.05;4.23)	-	-	-	-	-	-	2.16 (1.11;4.23)
ISAR-REACT 5	1.35 (0.97;1.86)***	1.32 (0.79;2.2)***	1.43 (0.93;2.21)	1.43 (0.94;2.19)	1.3 (0.44;2.37)	1.78 (0.52;6.08)	1.9 (0.72;1.65)	-
POPular AGE	-	1.19 (0.6;2.37)	1.08 (0.68;1.72)	1 (0.63;1.57)	0.5 (0.17;1.46)	-	0.71 (0.47;1.08)	0.71 (0.54;0.94)****

*data for the sensitivity analysis were used from *Lindholm D et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J. 2014 Aug 14;35(31):2083-93.*

**excluded from the sensitivity analysis

***provided by Authors of ISAR-REACT 5

****data for the sensitivity analysis in the Supplement of the main paper