SUPPLEMENTAL MATERIAL

Navarese EP et al. Comparative efficacy and safety of oral P2Y12 inhibitors in acute coronary syndrome: Network meta-analysis of 52,816 patients from 12 randomized trials. Circulation 2020.

Figure IA. PRISMA Flow Diagram

PRISMA 2009 Flow Diagram

Identification

Records identified through database searching (n =7,398)

Additional records identified through other sources (n =103)

Records after duplicates removed (n =6,057)

Screening

Records screened (n = 6,057)

Records excluded (n = 6,016)

Eligibility

Full-text articles assessed for eligibility (n = 41)

Full-text articles excluded, with reasons (n = 29)

primarily designed for analysis of platelet reactivity (16)
non-randomized design (9)
investigating different regimens of P2Y12 inhibitors (4)

Included

Studies included in qualitative synthesis (n = 12)

Studies included in quantitative synthesis (meta-analysis) (n = 12)

Figure IB. Network of treatment comparisons.

Prasugrel
n = 15 514

Clopidogrel
n = 23 758

Ticagrelor
n = 13 544

Nodes denote P2Y12 inhibitor type; thickness of link indicates number of direct comparisons

Figure IIA. Network meta-analysis of randomized trials for all-cause mortality.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

No. of Trials	12
No. of Pairwise comparison	12
I^2	21.7%

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.92	[0.84; 1.02]
Ticagrelor	0.83	[0.75; 0.92]

0.8   1   1.25

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	1.21	[1.09; 1.34]
Prasugrel	1.12	[0.98; 1.28]
Ticagrelor	1	

0.8   1   1.25

Prasugrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1.08	[0.98; 1.20]
Prasugrel	1	
Ticagrelor	0.90	[0.78; 1.03]

0.8   1   1.25

Figure IIB. Pairwise meta-analysis of randomized trials for all-cause mortality.
Individual and summary hazard ratios with 95% confidence intervals(CIs). ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, PRASFIT-ACS – PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 – Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

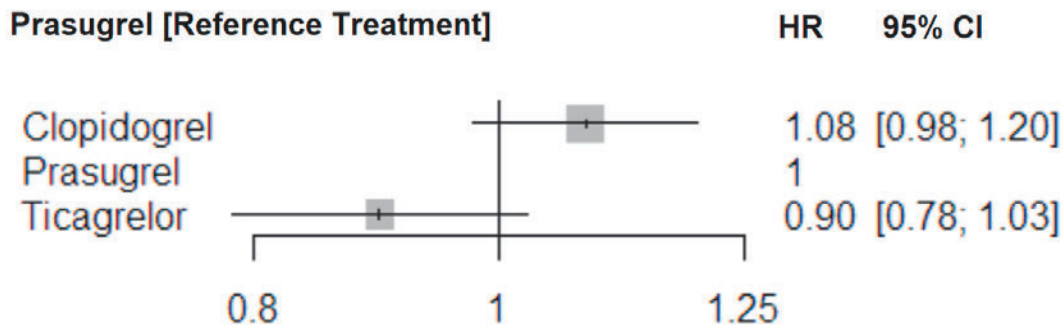| Group by Comparison	Trial, Year	Statistics for each study			
		Hazard ratio	Lower limit	Upper limit	p-Value
Prasugrel v Clopidogrel	The Elderly ACS II, 2018 [21]	1.31	0.80	2.14	0.28
	The PRASFIT-ACS, 2013 [19]	0.96	0.42	2.21	0.92
	TRILOGY ACS, 2012 [20]	0.94	0.82	1.08	0.38
	TRITON-TIMI 38, 2009 [10]	0.95	0.78	1.16	0.61
		0.96	0.86	1.07	0.45
Prasugrel v Ticagrelor	ISAR-REACT 5, 2019 [11]	0.81	0.60	1.10	0.19
	PRAGUE-18, 2017 [22]	1.13	0.66	1.93	0.65
		0.88	0.68	1.15	0.36
Ticagrelor v Clopidogrel	POPular AGE, 2019 [14]	0.92	0.57	1.47	0.72
	PHILO, 2015 [15]	1.42	0.54	3.74	0.48
	PLATO, 2009 [9]	0.78	0.69	0.89	0.00
	Tang et al., 2016 [17]	0.66	0.19	2.37	0.53
	Wang et al., 2016 [18]	0.53	0.24	1.19	0.12
	TICAKOREA, 2019 [16]	1.65	0.75	3.63	0.21
		0.80	0.71	0.90	0.00

0.1 0.2   0.5   1   2   5   10

Favors Treatment 1   Favors Treatment 2

Figure IIC. Network meta-analysis of randomized trials for non-cardiovascular mortality.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

No. of Trials	11
No. of Pairwise comparison	11
I^2	35.5%

Clopidogrel [Reference Treatment]   HR   95% CI

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.88	[0.75; 1.04]
Ticagrelor	0.97	[0.80; 1.16]

0.8   1   1.25

Ticagrelor [Reference Treatment]   HR   95% CI

	HR	95% CI
Clopidogrel	1.01	[0.7; 1.47]]
Prasugrel	0.89	[0.6; 1.31]]
Ticagrelor	1	

0.75   1   1.5

Prasugrel [Reference Treatment]   HR   95% CI

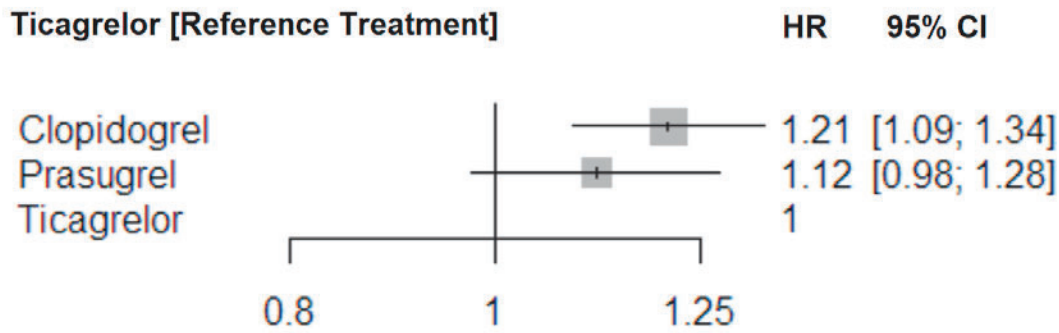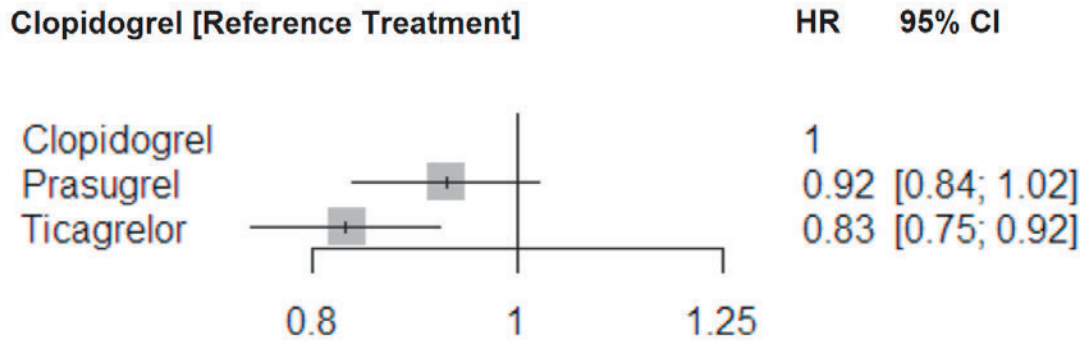|	HR	95% CI
Clopidogrel	1.13	[0.80; 1.61]
Prasugrel	1	
Ticagrelor	1.12	[0.76; 1.65]

0.75   1   1.5

Figure IID. Pairwise meta-analysis of randomized trials for non-cardiovascular mortality. Individual and summary hazard ratios with 95% confidence intervals (CIs).

ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 – Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.
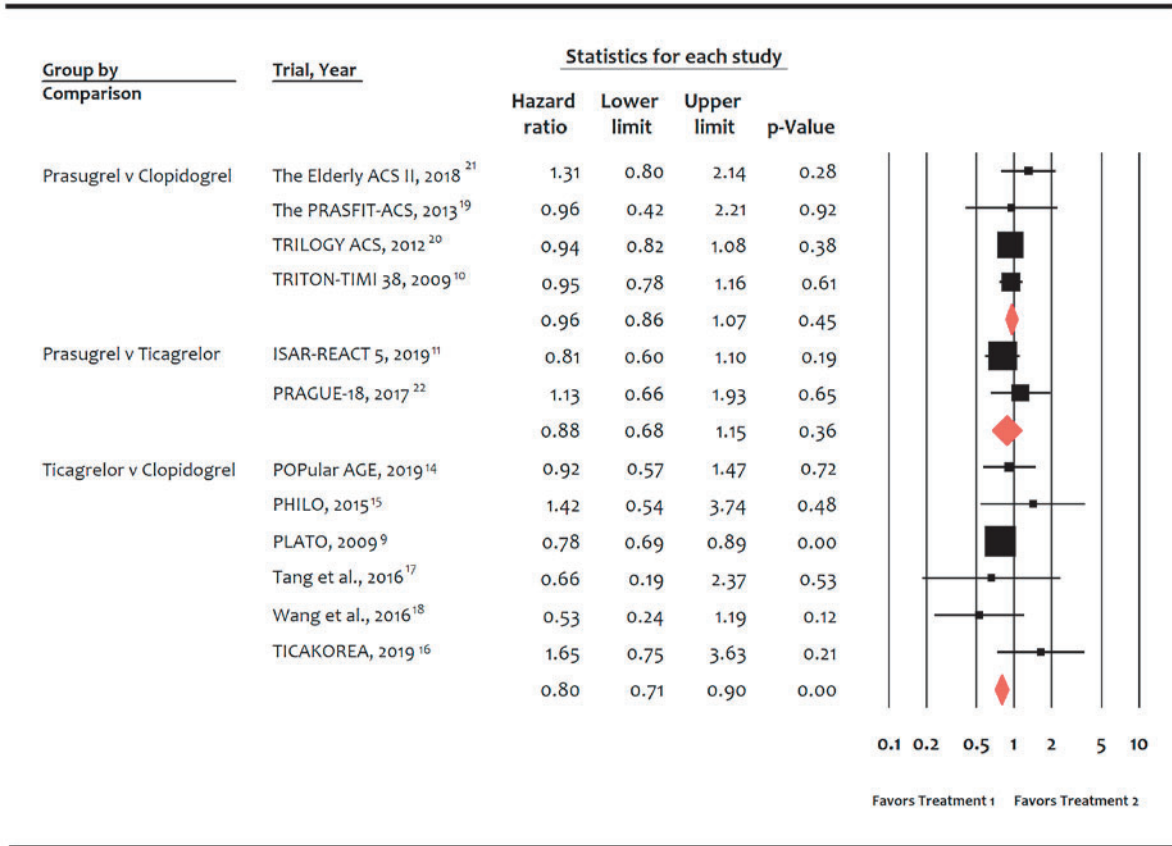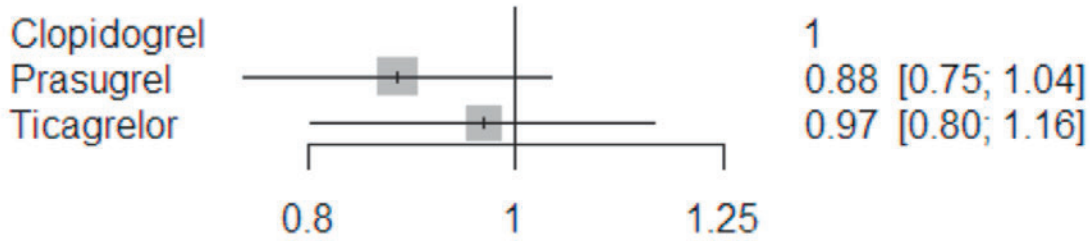
Group by Comparison	Trial, Year	Hazard ratio	Lower limit	Upper limit	p-Value
Prasugrel v Clopidogrel	TRILOGY ACS, 2012 [20]	0.97	0.71	1.33	0.85
	TRITON-TIMI 38, 2009 [10]	1.16	0.79	1.72	0.45
		1.04	0.81	1.33	0.75
Prasugrel v Ticagrelor	ISAR-REACT 5, 2019 [11]	0.63	0.46	0.86	0.00
	PRAGUE-18, 2017 [22]	1.21	0.45	3.22	0.70
		0.73	0.42	1.28	0.27
Ticagrelor v Clopidogrel	POPular AGE, 2019 [14]	1.00	0.51	1.95	1.00
	PHILO, 2015 [15]	3.00	0.12	73.31	0.50
	PLATO, 2009 [9]	0.71	0.49	1.03	0.07
	Tang et al., 2016 [17]	1.00	0.06	15.86	1.00
	TICAKOREA, 2019 [16]	0.26	0.03	2.28	0.22
		0.77	0.56	1.06	0.10

Favors Treatment 1   Favors Treatment 2

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Figure IIIA. Network meta-analysis of randomized trials for definite stent thrombosis.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

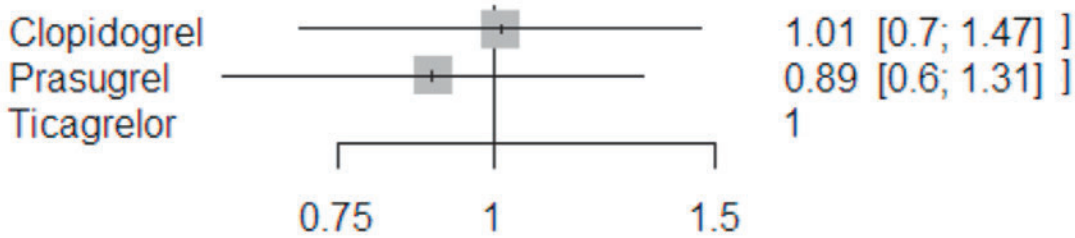| No. of Trials	4
No. of Pairwise comparison	4
I^2	0%

Clopidogrel [Reference Treatment]   HR   95% CI

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.40	[0.21; 0.77]
Ticagrelor	0.67	[0.50; 0.89]

0.5   1   2

Ticagrelor [Reference Treatment]   HR   95% CI

	HR	95% CI
Clopidogrel	1.50	[1.13; 2.01]
Prasugrel	0.60	[0.34; 1.08]
Ticagrelor	1	

0.5   1   2

Prasugrel [Reference Treatment]   HR   95% CI

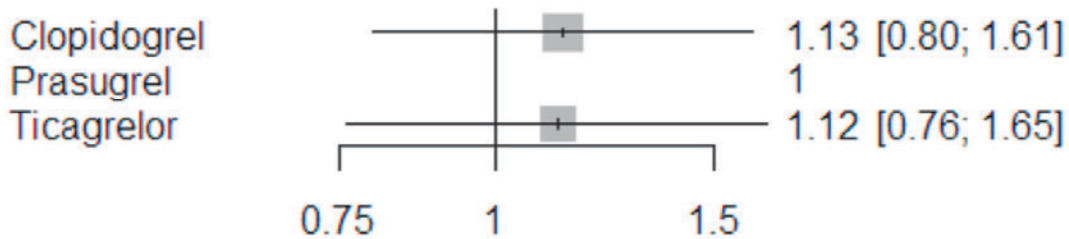|	HR	95% CI
Clopidogrel	2.49	[1.30; 4.74]
Prasugrel	1	
Ticagrelor	1.65	[0.93; 2.94]

0.5   1   2

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Figure IIIB. Pairwise meta-analysis of randomized trials for definite stent thrombosis.
Individual and summary hazard ratios with 95% confidence intervals (CIs). ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PLATO – PLATelet inhibition and patient Outcomes, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management.

Group by Comparison	Trial, Year	Statistics for each study				
		Hazard ratio	Lower limit	Upper limit	p-Value	
Prasugrel v Ticagrelor	ISAR-REACT 5, 2019 [11]	0.55	0.27	1.11	0.10	
	PRAGUE-18, 2017 [22]	0.73	0.27	1.97	0.53	
		0.60	0.34	1.07	0.09	
Ticagrelor v Clopidogrel	PLATO, 2009 [9]	0.67	0.50	0.90	0.01	
	TICAKOREA, 2019 [16]	0.51	0.09	2.84	0.44	
		0.66	0.49	0.89	0.01	

0.1 0.2 0.5 1 2 5 10

Favors Treatment 1   Favors Treatment 2
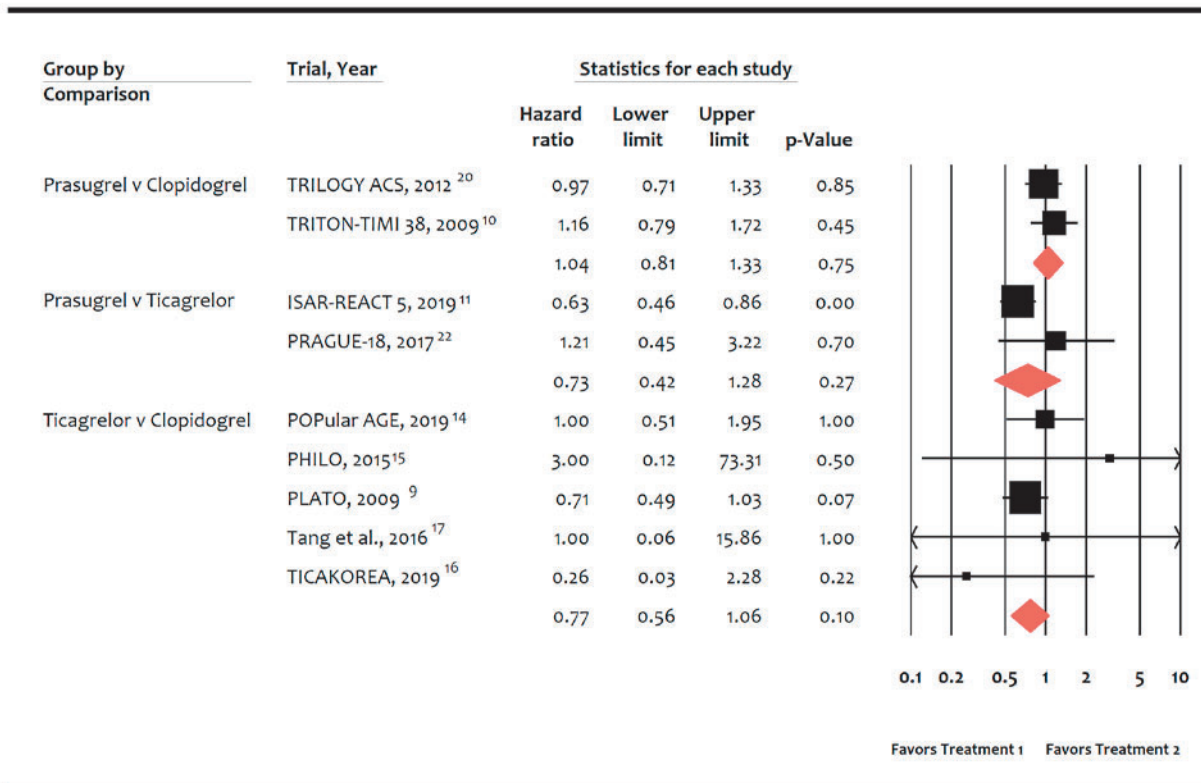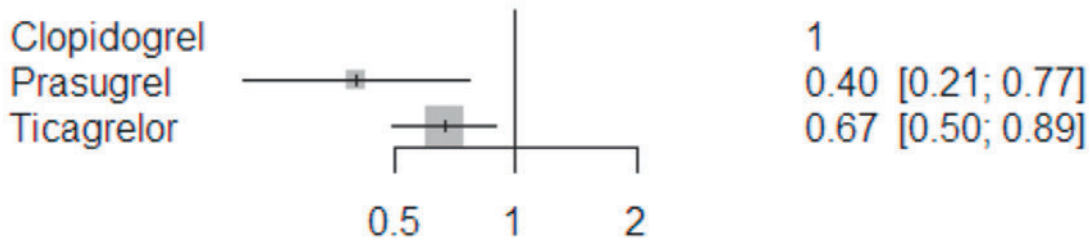
Figure IVA. Network meta-analysis of randomized trials for stroke.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

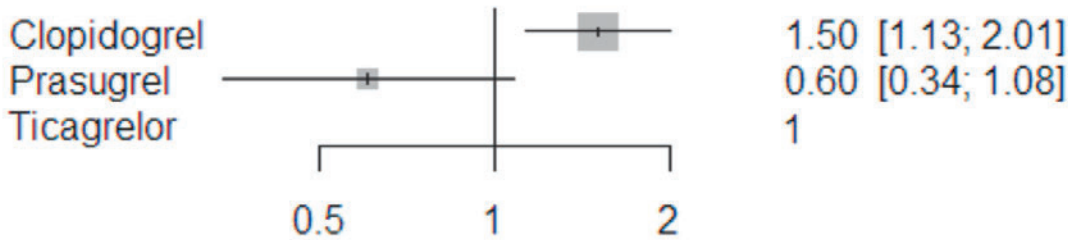| No. of Trials	11
No. of Pairwise comparison	11
I^2	0%

Clopidogrel [Reference Treatment] HR 95% CI

		HR	95% CI
Clopidogrel		1	
Prasugrel		0.92	[0.74; 1.15]
Ticagrelor		1.12	[0.90; 1.40]

0.8 1 1.25

Ticagrelor [Reference Treatment] HR 95% CI

		HR	95% CI
Clopidogrel		0.89	[0.72; 1.12]
Prasugrel		0.82	[0.62; 1.10]
Ticagrelor		1	

0.75 1 1.5

Prasugrel [Reference Treatment] HR 95% CI

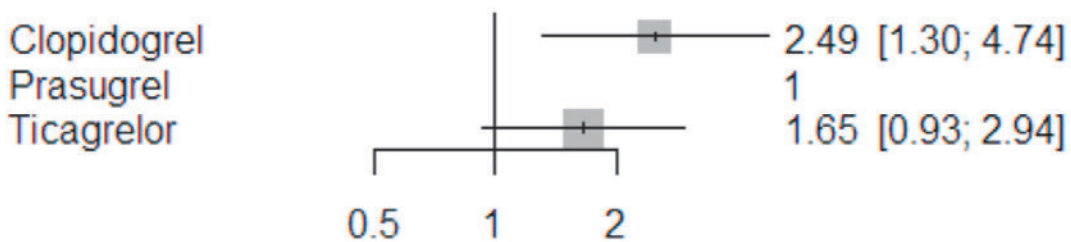|		HR	95% CI
Clopidogrel		1.08	[0.87; 1.35]
Prasugrel		1	
Ticagrelor		1.21	[0.91; 1.61]

0.75 1 1.5

Figure IVB. Pairwise meta-analysis of randomized trials for stroke.
Individual and summary hazard ratios with 95% confidence intervals (CIs). ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, PRASFIT-ACS – PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 – Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

Group by Comparison	Trial, Year	Statistics for each study				
		Hazard ratio	Lower limit	Upper limit	p-Value	
Prasugrel v Clopidogrel	The Elderly ACS II, 2018 [21]	0.55	0.22	1.37	0.20	
	The PRASFIT-ACS, 2013 [19]	0.60	0.22	1.64	0.32	
	TRILOGY ACS, 2012 [20]	0.89	0.63	1.26	0.51	
	TRITON-TIMI 38, 2009 [10]	1.02	0.71	1.46	0.91	
		0.90	0.71	1.13	0.35	
Prasugrel v Ticagrelor	ISAR-REACT 5, 2019 [11]	0.85	0.46	1.58	0.62	
	PRAGUE-18, 2017 [22]	1.65	0.48	5.66	0.43	
		0.97	0.56	1.69	0.93	
Ticagrelor v Clopidogrel	PHILO, 2015 [15]	1.50	0.54	4.20	0.44	
	PLATO, 2009 [9]	1.17	0.91	1.51	0.23	
	Tang et al., 2016 [17]	0.20	0.02	1.73	0.14	
	Wang et al., 2016 [18]	0.62	0.10	3.79	0.60	
	TICAKOREA, 2019 [16]	1.25	0.38	4.10	0.71	
		1.15	0.91	1.46	0.25	

0.1 0.2   0.5   1   2   5   10
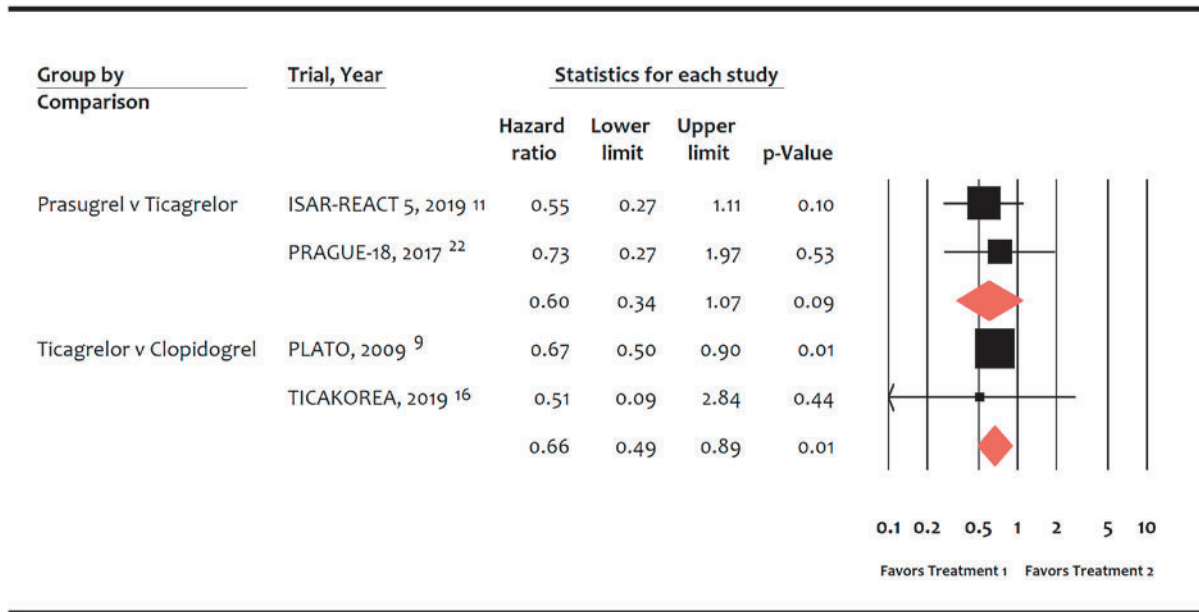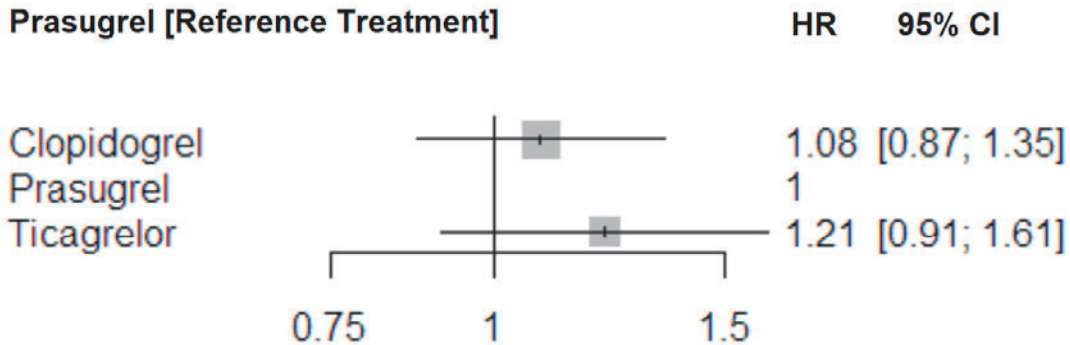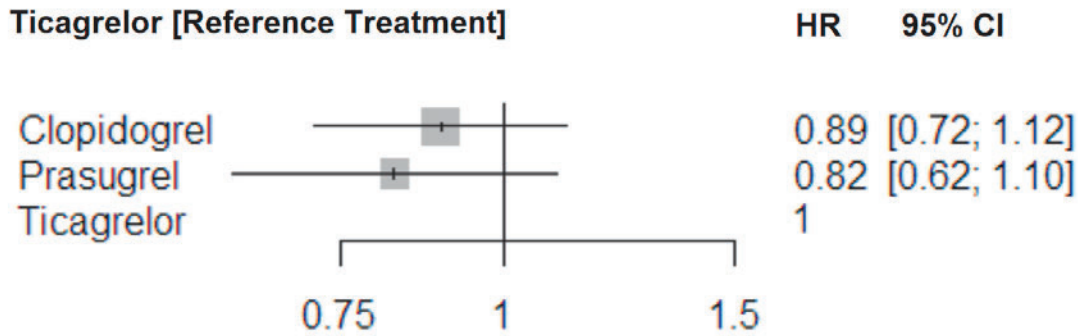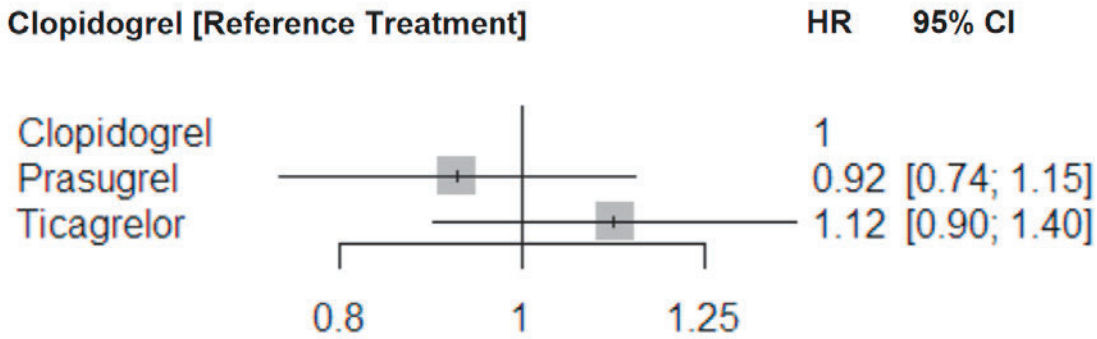
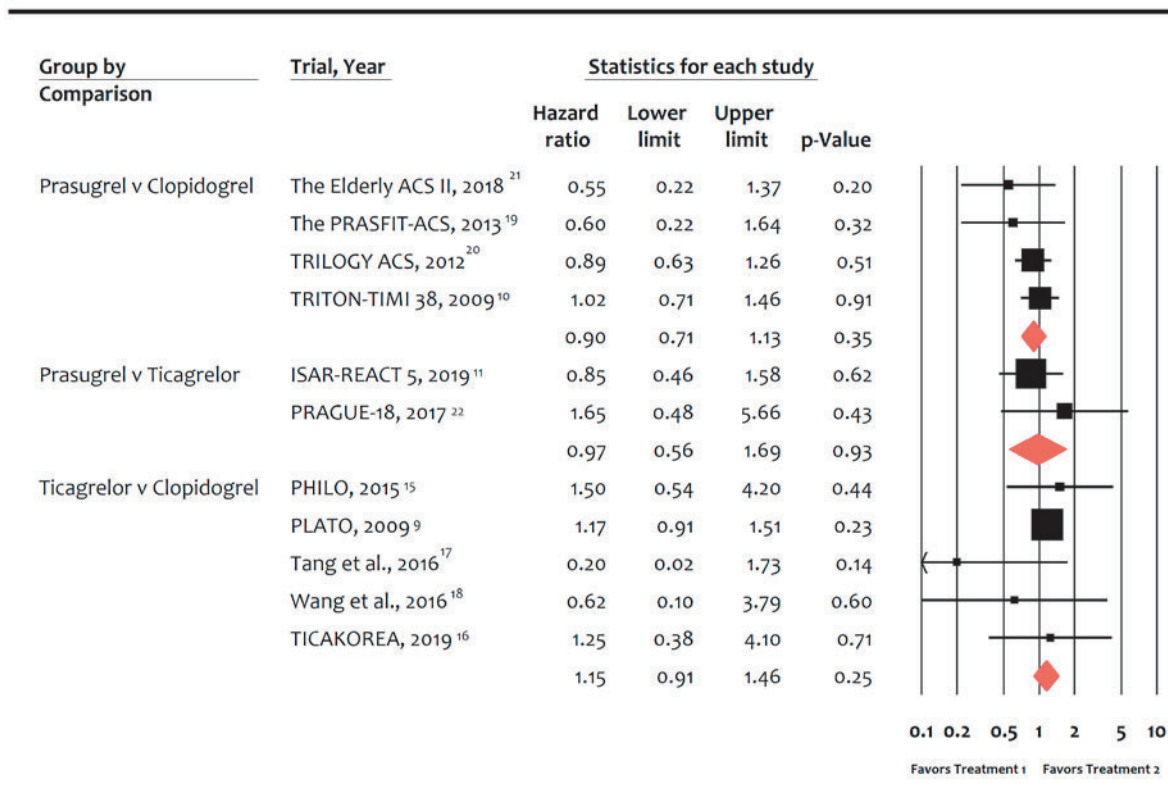Favors Treatment 1   Favors Treatment 2

Figure VA. Network meta-analysis of randomized trials for hemorrhagic stroke.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

No. of Trials	4
No. of Pairwise comparison	4
I^2	0%

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.48	[0.10; 2.21]
Ticagrelor	1.59	[0.83; 3.03]

0.2 0.5 1 2 5

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	0.63	[0.33; 1.21]
Prasugrel	0.30	[0.07; 1.28]
Ticagrelor	1	

0.1 0.5 1 2 10

Prasugrel [Reference Treatment]

	HR	95% CI
Clopidogrel	2.08	[0.45; 9.58]
Prasugrel	1	
Ticagrelor	3.30	[0.78; 13.97]

0.1 0.5 1 2 10

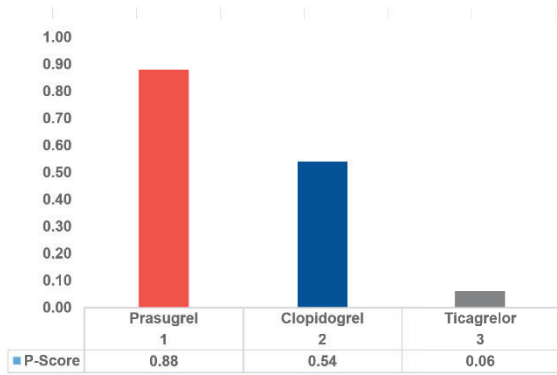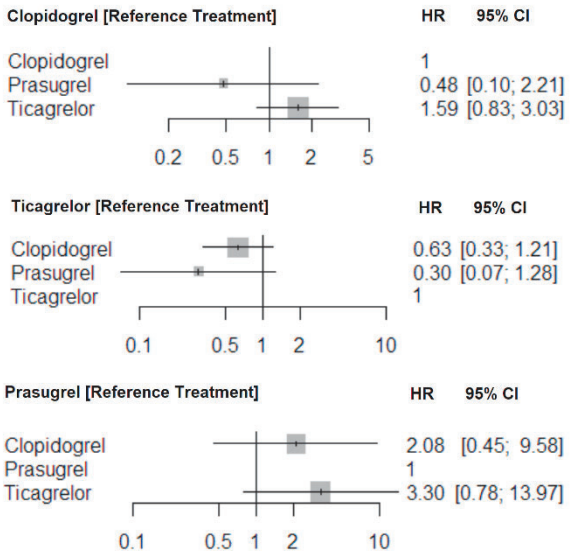|	Prasugrel 1	Clopidogrel 2	Ticagrelor 3
P-Score	0.88	0.54	0.06

Figure VB. Network meta-analysis for ischemic stroke.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

No. of Trials	4
No. of Pairwise comparison	4
I^2	0%

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.94	[0.52; 1.72]
Ticagrelor	1.04	[0.79; 1.38]

0.75   1   1.5

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	0.96	[0.72; 1.27]
Prasugrel	0.90	[0.51; 1.61]
Ticagrelor	1	

0.75   1   1.5

Prasugrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1.06	[0.58; 1.94]
Prasugrel	1	
Ticagrelor	1.11	[0.62; 1.97]

0.75   1   1.5

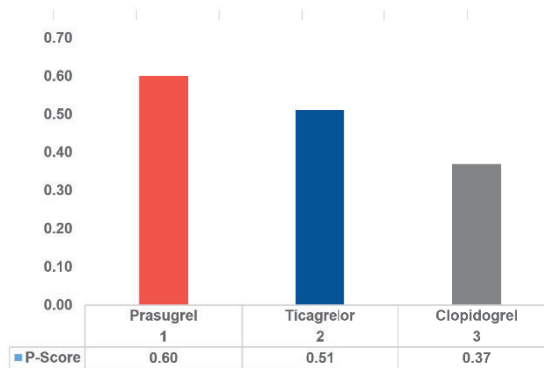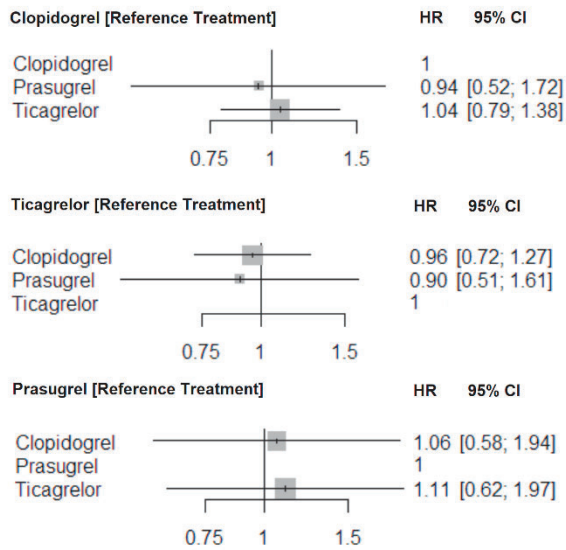|	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.60	0.51	0.37

13

Figure VIA. Pairwise meta-analysis of randomized trials for PLATO major bleeding.
Individual and summary hazard ratios with 95% confidence intervals(CIs). PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management.

Group by Comparison		Statistics for each study				
		Hazard ratio	Lower limit	Upper limit	p-Value	
Ticagrelor v Clopidogrel	PHILO [15]	0.99	0.89	1.10	0.85	
	PLATO [9]	1.04	0.95	1.13	0.38	
	TICAKOREA [16]	1.89	1.03	3.47	0.04	
	Wang et al. [18]	1.25	0.43	3.62	0.68	
		1.04	0.93	1.15	0.50	

0.1 0.2   0.5   1   2   5   10

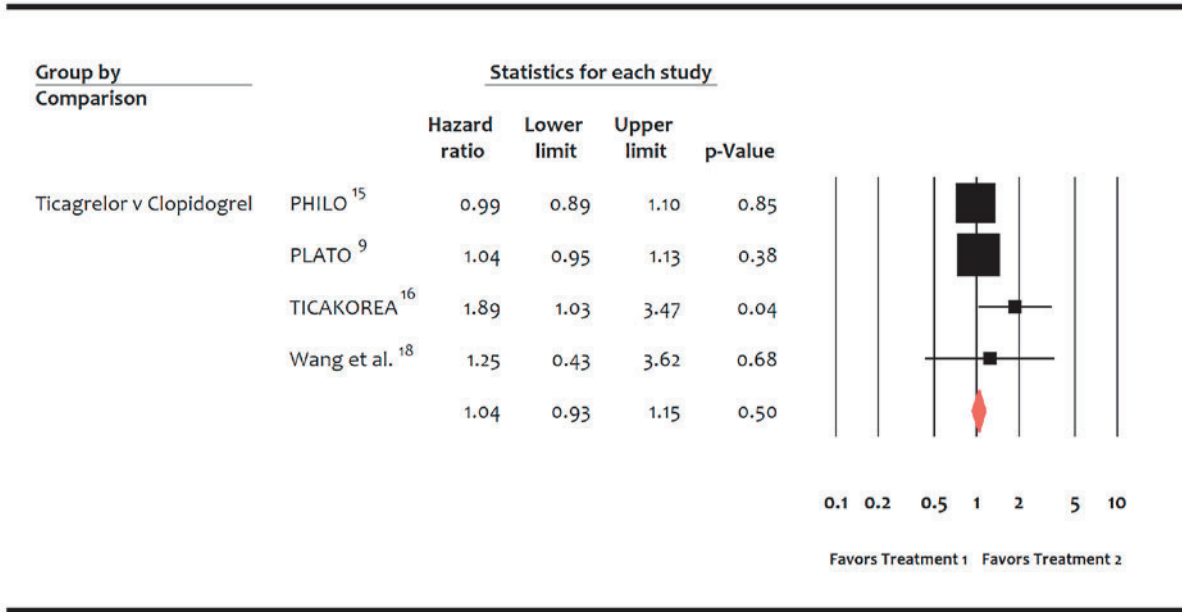Favors Treatment 1   Favors Treatment 2

Figure VIB. Pairwise meta-analysis of randomized trials for TIMI major bleeding.
Individual and summary hazard ratios with 95% confidence intervals(CIs). TICAKOREA – Ticagrelor Versus
Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted
Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 –
Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in
Myocardial Infarction 38.

Group by Comparison	Study name	Statistics for each study				
		Hazard ratio	Lower limit	Upper limit	p-Value	
Prasugrel v Clopidogrel	TRITON-TIMI 38, 2009 [10]	1.32	1.03	1.69	0.03	
	TRILOGY ACS, 2012 [20]	1.23	0.84	1.81	0.29	
		1.29	1.05	1.59	0.01	
Ticagrelor v Clopidogrel	PLATO, 2009 [9]	1.03	0.93	1.15	0.59	
	TICAKOREA, 2019 [16]	2.47	1.08	5.64	0.03	
	POPular AGE, 2019 [14]	0.41	0.17	0.99	0.05	
	Tang et al., 2016 [17]	0.20	0.01	4.17	0.30	
		0.95	0.47	1.94	0.89	

0.1 0.2   0.5   1   2   5   10

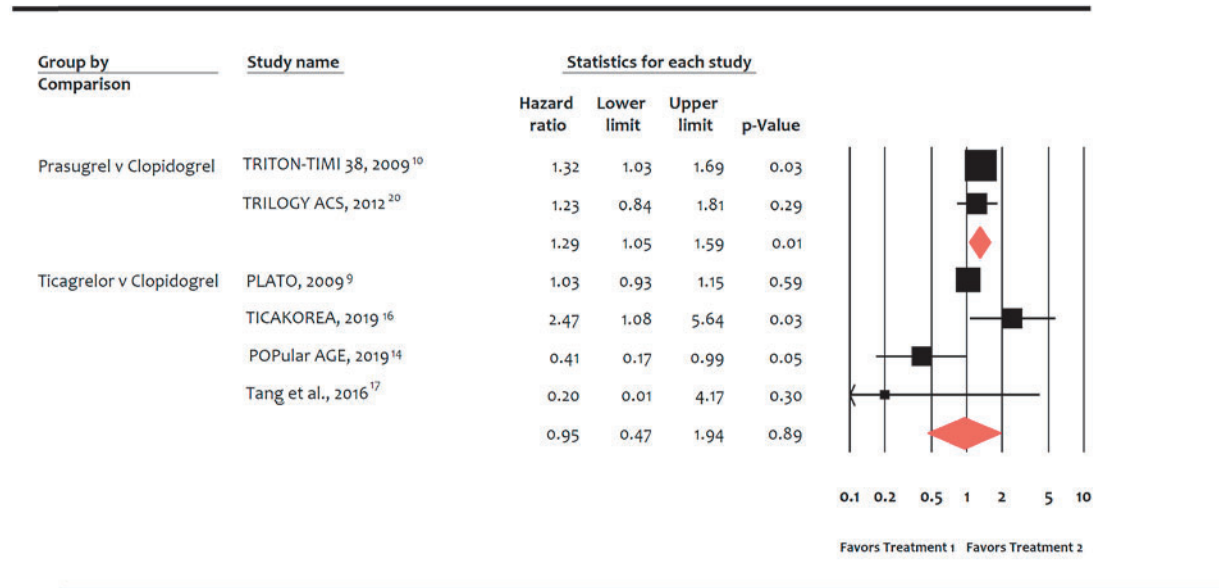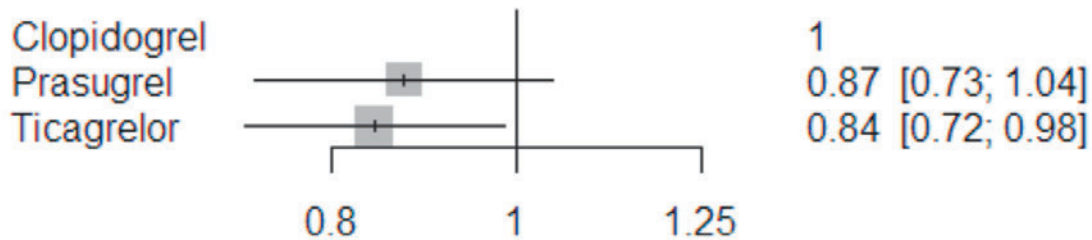Favors Treatment 1   Favors Treatment 2

Figure VIIA. Trials with planned invasive evaluation - Cardiovascular mortality.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.
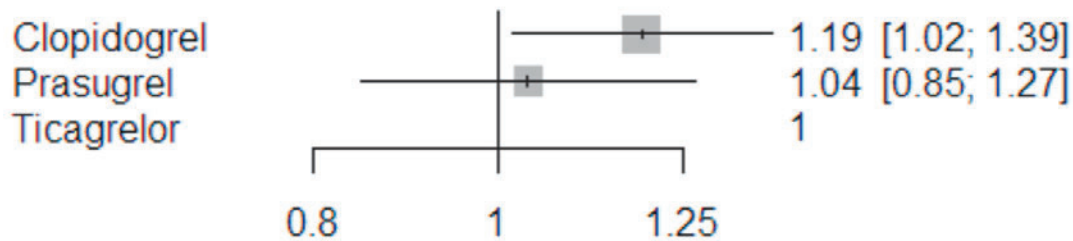
Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.87	[0.73; 1.04]
Ticagrelor	0.84	[0.72; 0.98]

0.8   1   1.25

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	1.19	[1.02; 1.39]
Prasugrel	1.04	[0.85; 1.27]
Ticagrelor	1	

0.8   1   1.25

Prasugrel [Reference Treatment]

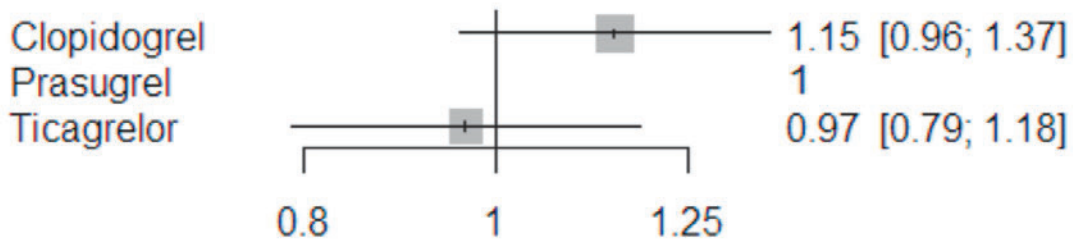|	HR	95% CI
Clopidogrel	1.15	[0.96; 1.37]
Prasugrel	1	
Ticagrelor	0.97	[0.79; 1.18]

0.8   1   1.25

Figure VIIB. Trials with planned invasive evaluation - All-cause mortality.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.92	[0.79; 1.08]
Ticagrelor	0.88	[0.76; 1.03]

0.8   1   1.25

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	1.14	[0.98; 1.32]
Prasugrel	1.05	[0.87; 1.26]
Ticagrelor	1	

0.8   1   1.25

Prasugrel [Reference Treatment]

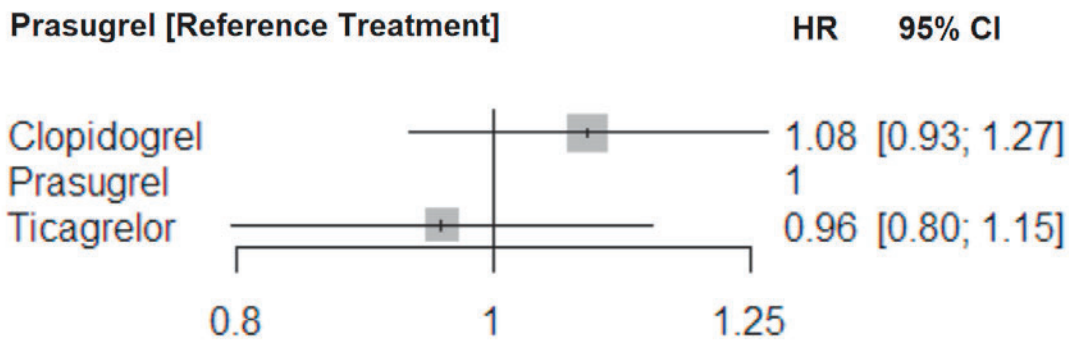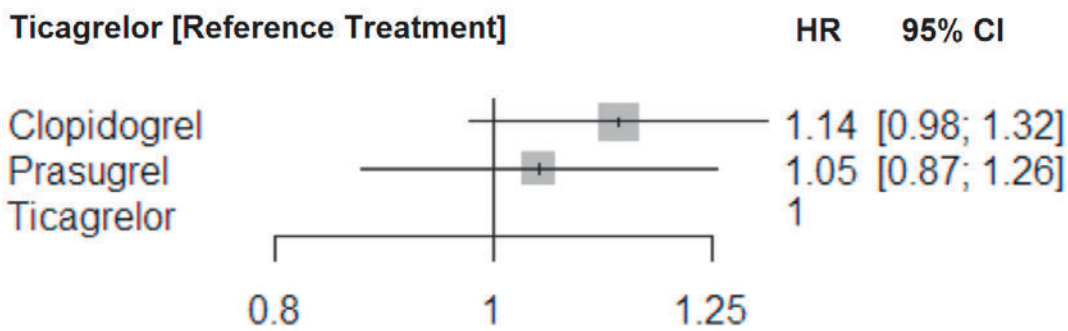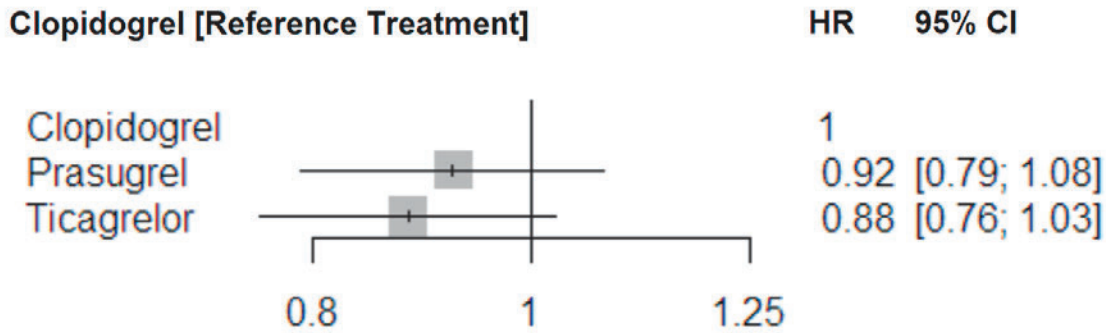|	HR	95% CI
Clopidogrel	1.08	[0.93; 1.27]
Prasugrel	1	
Ticagrelor	0.96	[0.80; 1.15]

0.8   1   1.25

Figure VIIC. Trials with planned invasive evaluation - Myocardial infarction.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]　　　　　　　　　　HR　　95% CI

		HR	95% CI
Clopidogrel		1	
Prasugrel		0.76	[0.59; 0.96]
Ticagrelor		0.95	[0.72; 1.26]

0.75　　　1　　　　1.5

Ticagrelor [Reference Treatment]　　　　　　　　　　HR　　95% CI

		HR	95% CI
Clopidogrel		1.05	[0.79; 1.38]
Prasugrel		0.79	[0.59; 1.06]
Ticagrelor		1	

0.75　　　1　　　　1.5

Prasugrel [Reference Treatment]　　　　　　　　　　HR　　95% CI

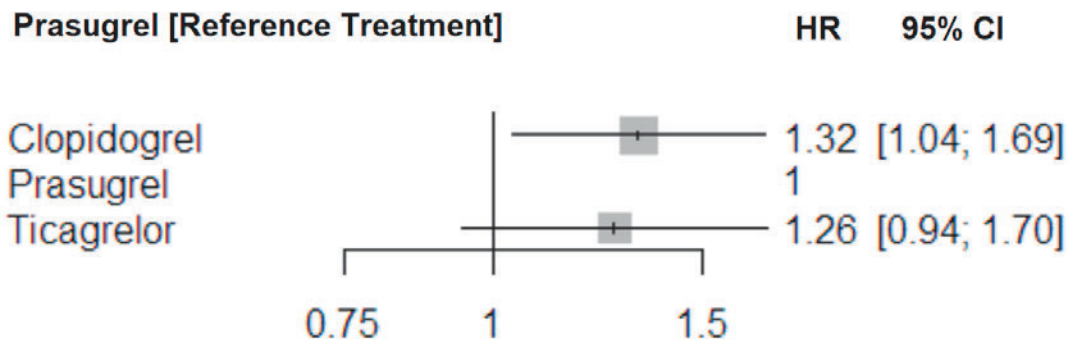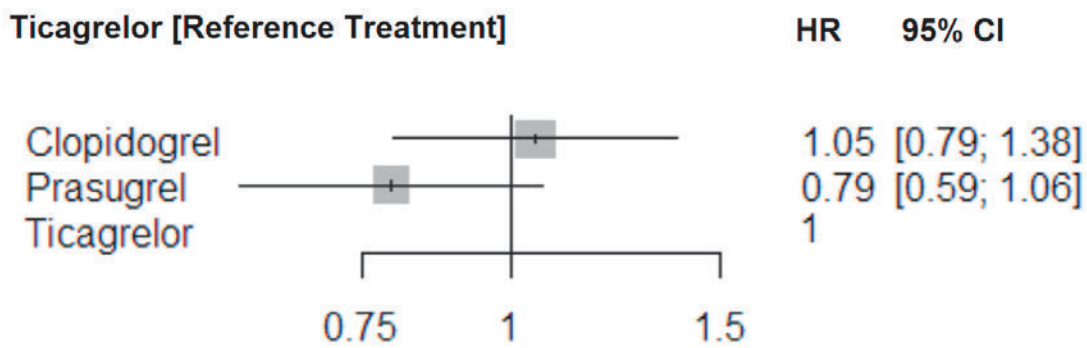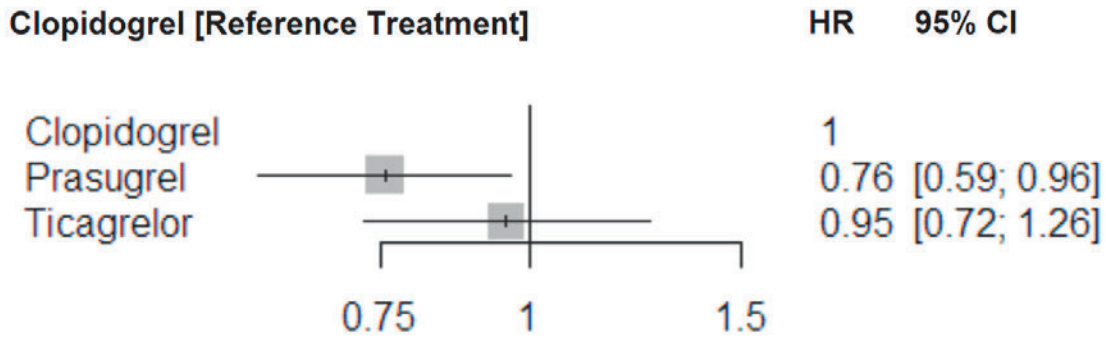|		HR	95% CI
Clopidogrel		1.32	[1.04; 1.69]
Prasugrel		1	
Ticagrelor		1.26	[0.94; 1.70]

0.75　　　1　　　　1.5

Figure VIID. Trials with planned invasive evaluation - Definite or probable stent thrombosis.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.49	[0.38; 0.64]
Ticagrelor	0.71	[0.56; 0.90]

0.5   1   2

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	1.41	[1.11; 1.78]
Prasugrel	0.69	[0.51; 0.95]
Ticagrelor	1	

0.75   1   1.5

Prasugrel [Reference Treatment]

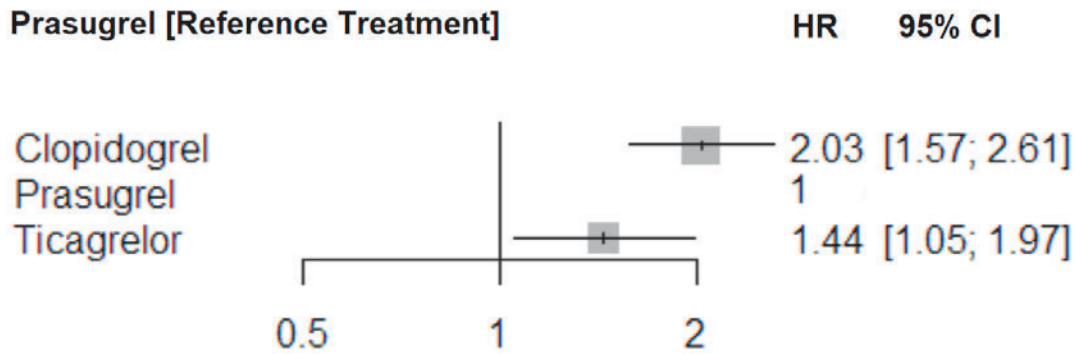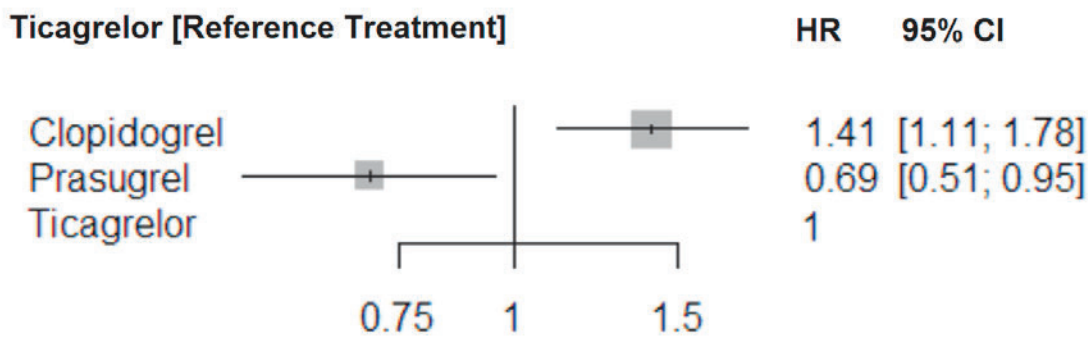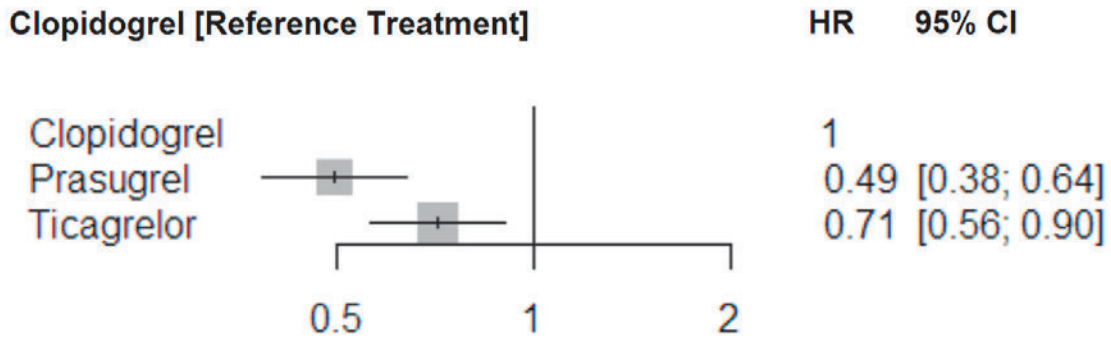|	HR	95% CI
Clopidogrel	2.03	[1.57; 2.61]
Prasugrel	1	
Ticagrelor	1.44	[1.05; 1.97]

0.5   1   2

Figure VIIE. Trials with planned invasive evaluation - Definite stent thrombosis.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]   HR   95% CI

Clopidogrel	1	
Prasugrel	0.39	[0.20; 0.75]
Ticagrelor	0.64	[0.46; 0.89]

0.2   0.5   1   2   5

Ticagrelor [Reference Treatment]   HR   95% CI

Clopidogrel	1.57	[1.12; 2.19]
Prasugrel	0.60	[0.34; 1.08]
Ticagrelor	1	

0.5   1   2

Prasugrel [Reference Treatment]   HR   95% CI

Clopidogrel	2.59	[1.33; 5.05]
Prasugrel	1	
Ticagrelor	1.65	[0.93; 2.94]

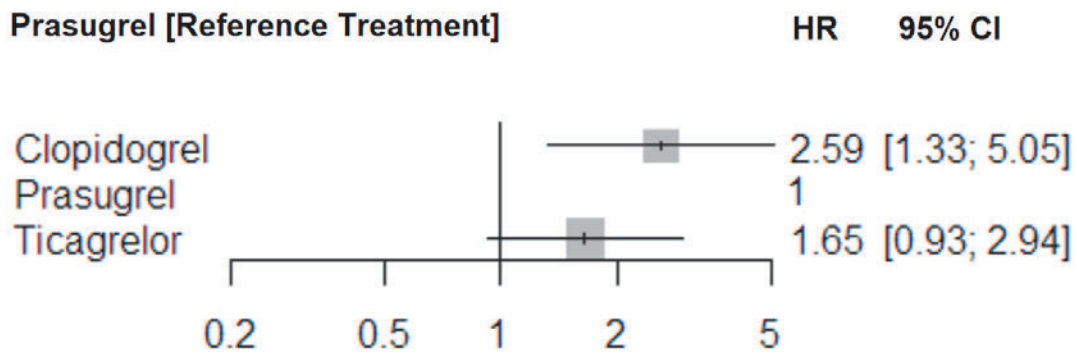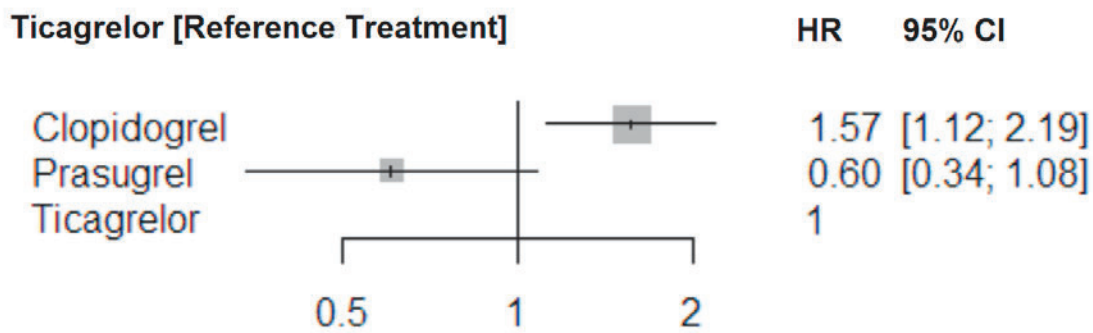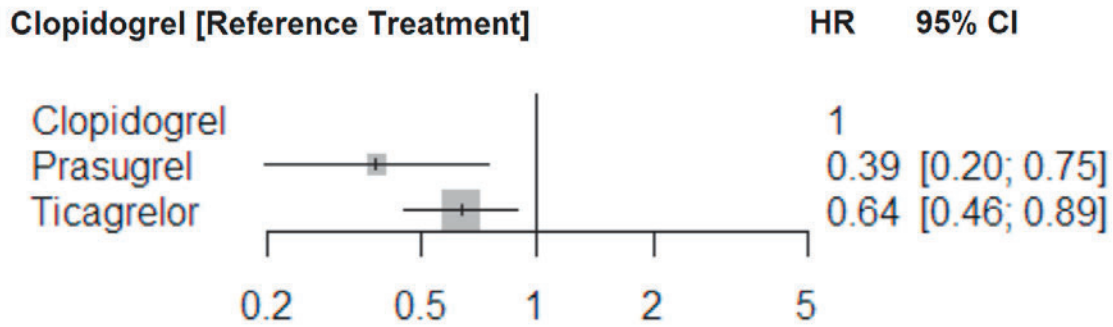0.2   0.5   1   2   5

Figure VIIF. Trials with planned invasive evaluation – Stroke.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	0.93	[0.70; 1.23]
Ticagrelor	1.05	[0.79; 1.39]

0.8   1   1.25

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	0.96	[0.72; 1.27]
Prasugrel	0.89	[0.63; 1.25]
Ticagrelor	1	

0.75   1   1.5

Prasugrel [Reference Treatment]

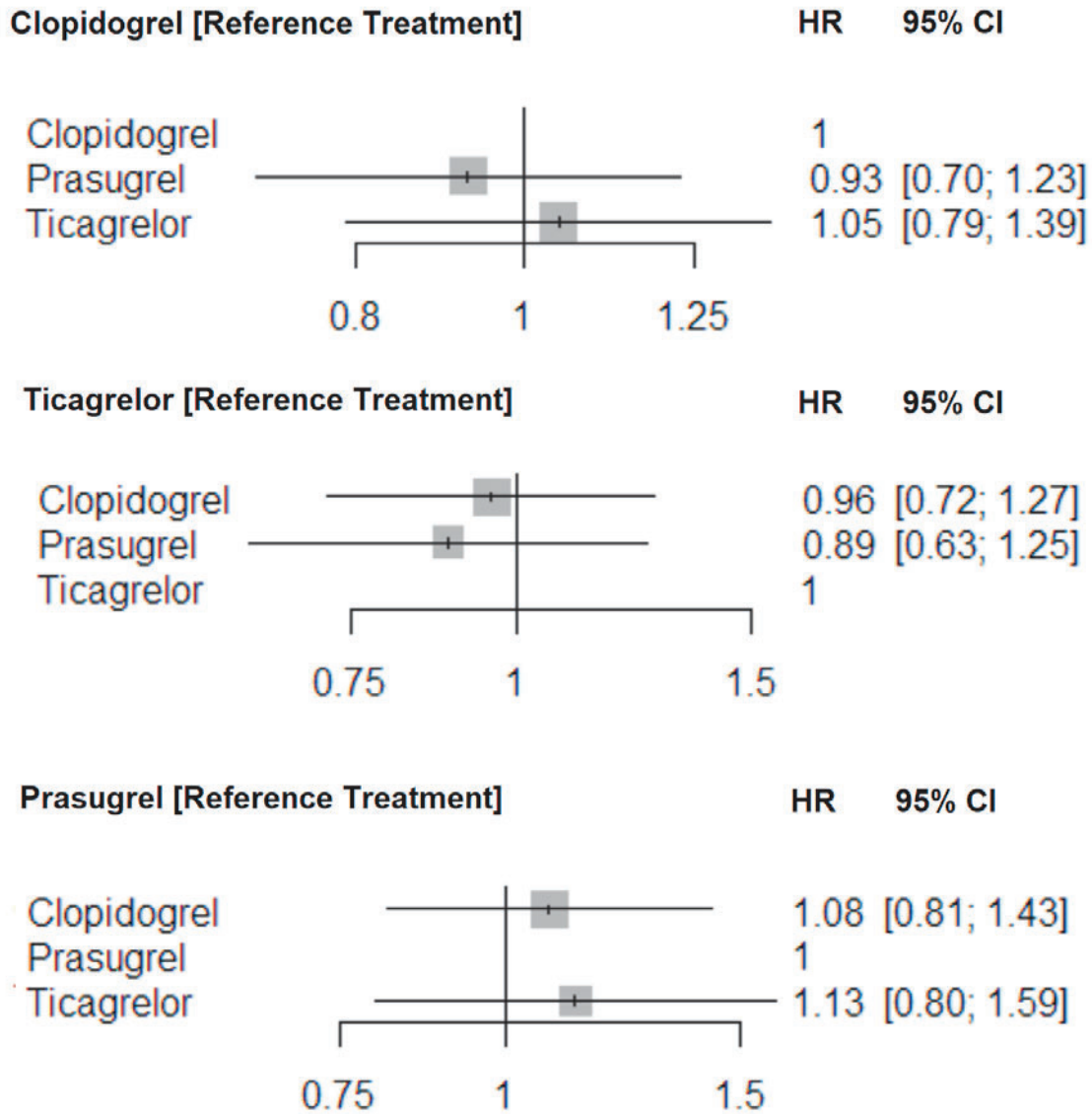|	HR	95% CI
Clopidogrel	1.08	[0.81; 1.43]
Prasugrel	1	
Ticagrelor	1.13	[0.80; 1.59]

0.75   1   1.5

Figure VIIG. Trials with planned invasive evaluation - Major bleeding.
Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) determined by network meta-analysis.

Clopidogrel [Reference Treatment]

	HR	95% CI
Clopidogrel	1	
Prasugrel	1.19	[0.93; 1.53]
Ticagrelor	1.15	[0.91; 1.44]

0.75   1   1.5

Ticagrelor [Reference Treatment]

	HR	95% CI
Clopidogrel	0.87	[0.69; 1.10]
Prasugrel	1.04	[0.82; 1.33]
Ticagrelor	1	

0.8   1   1.25

Prasugrel [Reference Treatment]

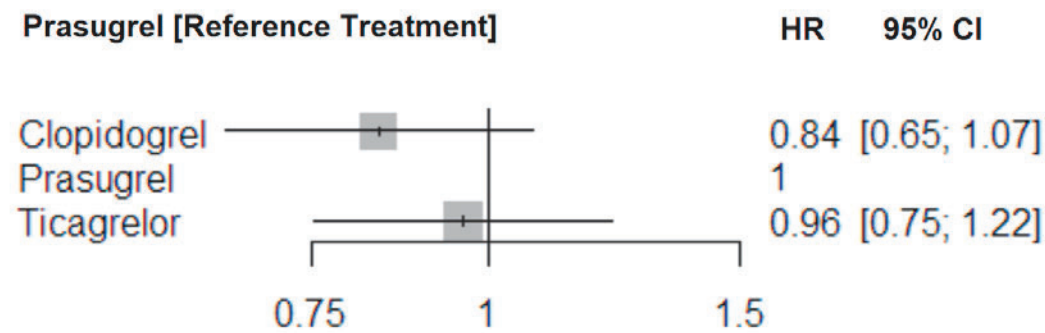|	HR	95% CI
Clopidogrel	0.84	[0.65; 1.07]
Prasugrel	1	
Ticagrelor	0.96	[0.75; 1.22]

0.75   1   1.5
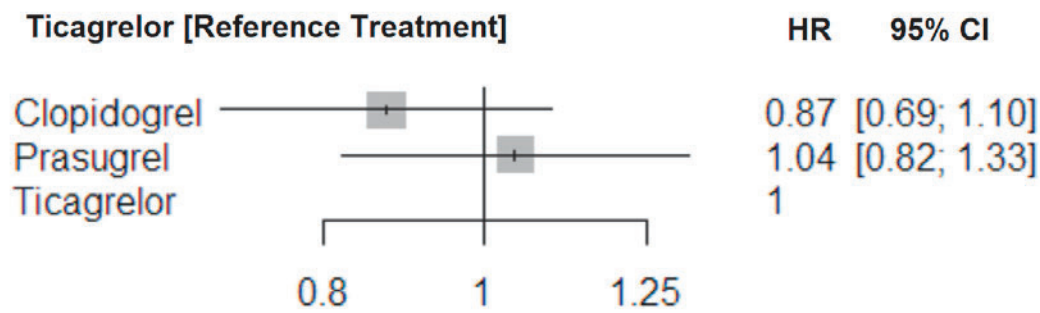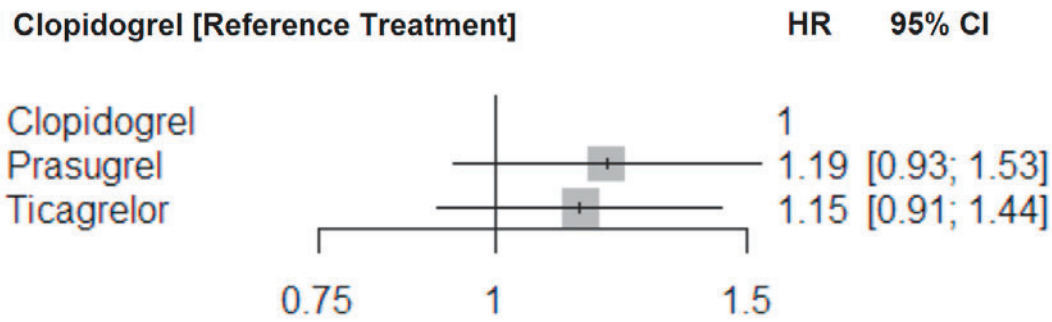
Figure VIII. Rankogram of antithrombotics for efficacy and safety.

All-cause mortality

	Ticagrelor 1	Prasugrel 2	Clopidogrel 3
P-Score	0.97	0.49	0.03

Cardiovascular mortality

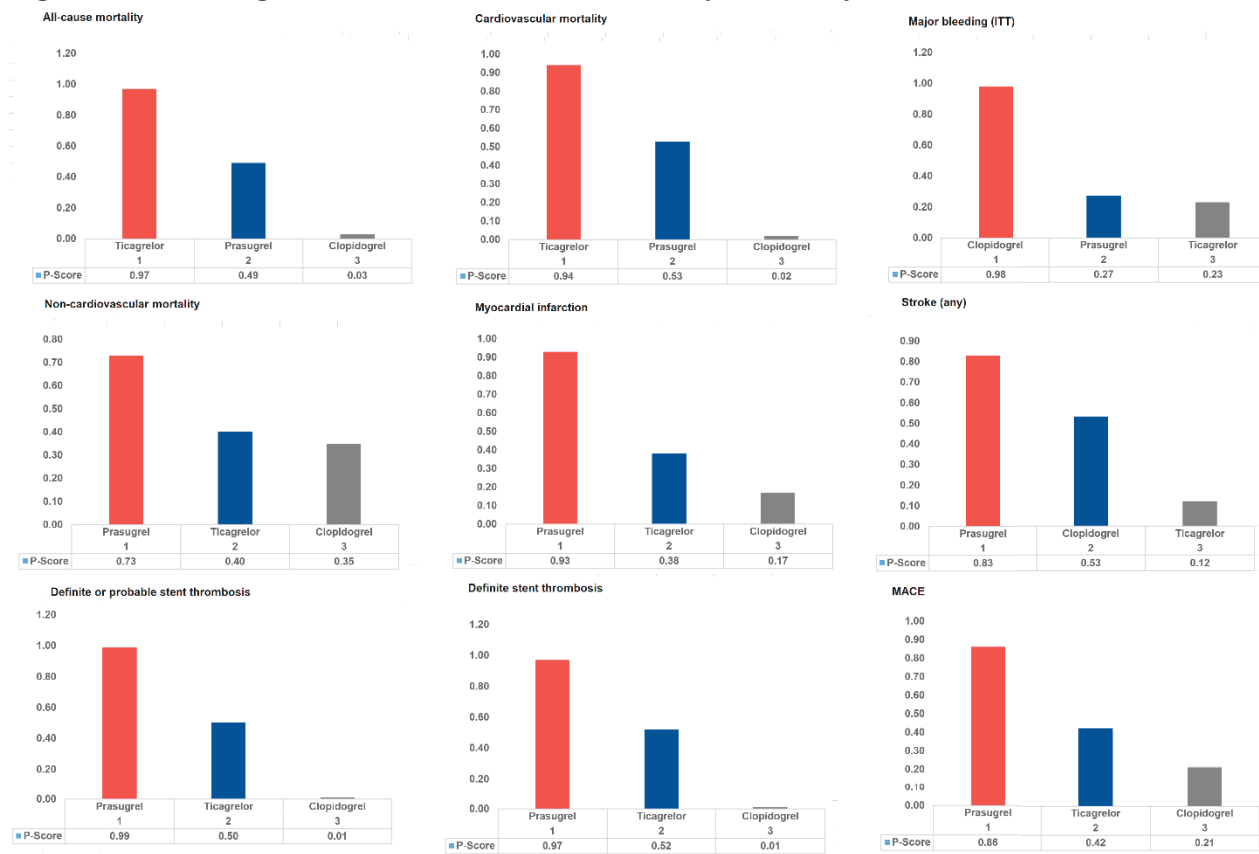|	Ticagrelor 1	Prasugrel 2	Clopidogrel 3
P-Score	0.94	0.53	0.02

Major bleeding (ITT)

	Clopidogrel 1	Prasugrel 2	Ticagrelor 3
P-Score	0.98	0.27	0.23

Non-cardiovascular mortality

	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.73	0.40	0.35

Myocardial infarction

	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.93	0.38	0.17

Stroke (any)

	Prasugrel 1	Clopidogrel 2	Ticagrelor 3
P-Score	0.83	0.53	0.12

Definite or probable stent thrombosis

	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.99	0.50	0.01

Definite stent thrombosis

	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.97	0.52	0.01

MACE

	Prasugrel 1	Ticagrelor 2	Clopidogrel 3
P-Score	0.86	0.42	0.21

Table I. Electronic search using MEDLINE database.

Search	Query	Items found
#8	Search **((ticagrelor) AND acute coronary syndrome)** Filters: **Clinical Trial**	173
#7	Search **((prasugrel) AND acute coronary syndrome)** Filters: **Clinical Trial**	171
#6	Search **((clopidogrel) AND randomized controlled trial)** Filters: **Clinical Trial**	1586
#5	Search **((prasugrel) AND randomized controlled trial)** Filters: **Clinical Trial**	307
#4	Search **((ticagrelor) AND randomized controlled trial)** Filters: **Clinical Trial**	361
#3	Search **((p2y12 inhibitor) AND randomized controlled trial)** Filters: **Clinical Trial**	109
#2	Search **(((ticagrelor) OR prasugrel) OR clopidogrel)** Filters: **Clinical Trial**	2279
#1	Search **((clopidogrel) AND acute coronary syndrome)** Filters: **Clinical Trial**	473

Table II. Assessment of Consistency of Network Meta-Analysis Model

Comparison	k	Prop	nma	Direct	Indirect	ROR	Z	P-value
All-cause mortality								
Clopidogrel: Prasugrel	4	0.83	1.23	1.19	1.47	0.80	-0.81	0.41
Clopidogrel: Ticagrelor	6	0.75	1.02	1.08	0.87	1.23	0.81	0.41
Prasugrel: Ticagrelor	2	0.42	0.83	0.73	0.90	0.80	-0.81	0.41
Cardiovascular mortality								
Clopidogrel: Prasugrel	4	0.85	1.11	1.09	1.25	0.86	-0.69	0.49
Clopidogrel: Ticagrelor	6	0.81	1.19	1.23	1.07	1.15	0.69	0.49
Prasugrel: Ticagrelor	2	0.34	1.07	0.98	1.12	0.86	-0.69	0.91
Myocardial infarction.								
Clopidogrel: Prasugrel	4	0.83	1.23	1.19	1.47	0.80	-0.81	0.41
Clopidogrel: Ticagrelor	6	0.75	1.02	1.08	0.87	1.23	0.81	0.41
Prasugrel: Ticagrelor	2	0.42	0.83	0.73	0.90	0.80	-0.81	0.41
Stroke								
Clopidogrel: Prasugrel	4	0.83	1.07	1.02	1.35	0.75	-1.41	0.15
Clopidogrel: Ticagrelor	6	0.78	1.13	1.21	0.91	1.32	1.41	0.15
Prasugrel: Ticagrelor	2	0.39	1.06	0.89	1.18	0.75	-1.41	0.15
Definite or probable stent thrombosis								
Clopidogrel: Prasugrel	3	0.84	2.01	2.07	1.75	1.17	0.47	0.64
Clopidogrel: Ticagrelor	3	0.88	1.38	1.35	1.59	0.84	-0.47	0.64
Prasugrel: Ticagrelor	1	0.28	0.68	0.77	0.65	1.17	0.47	0.64
Definite stent thrombosis								
Clopidogrel: Prasugrel	0	0.00	2.01	2.48	.	0.00	.	.
Clopidogrel: Ticagrelor	2	0.88	1.00	1.50	1.50	1.50	.	.
Prasugrel: Ticagrelor	2	0.28	1.00	0.60	0.60	0.60	.	.
Non cardiovascular mortality								
Clopidogrel: Prasugrel	3	0.73	1.13	0.98	1.67	0.58	-1.31	0.18
Clopidogrel: Ticagrelor	6	0.67	1.01	1.20	0.70	1.69	1.31	0.18
Prasugrel: Ticagrelor	2	0.60	0.89	0.71	1.22	0.58	-1.31	0.18
Major bleeding								
Clopidogrel: Prasugrel	4	0.67	0.79	0.78	0.81	0.95	-0.19	0.84
Clopidogrel: Ticagrelor	6	0.74	0.78	0.79	0.76	1.04	0.19	0.84
Prasugrel: Ticagrelor	2	0.60	0.99	0.97	1.01	0.95	-0.19	0.84

Comparison = Treatment comparison; k =Number of studies providing direct evidence; prop= Proportion of direct evidence; nma =Estimated treatment effect (HR) in network meta-analysis; direct=Estimated treatment effect (HR) derived from direct evidence; Indirect =Estimated treatment effect (RR) 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 consistency

Table III. Egger's regression test

Outcome	P-value (2-tailed)
All-cause mortality	0.46
Major bleeding	0.25
Cardiovascular mortality	0.84
Myocardial infarction	0.99
Stroke	0.13
Definite or probable stent thrombosis	0.33
Definite stent thrombosis	0.80
MACE	0.94
Hemorrhagic stroke	0.32
Ischemic stroke	0.46
Non-cardiovascular mortality	0.34

Table IV. Patient characteristics.

Study	Arm	Age (years)	Male	Diabetes	Current smoker	Arterial hypertension	Hypercholesterolemia	STEMI	NSTEMI	UA or other	Coronary angiography	PCI	Medical therapy
[The Elderly ACS II trial][21] Savonitto et al. 2018 Circulation [NCT01777503]	prasugrel	80	419 (59%)	215 (30%)	62 (9%)	554 (78%)	332 (47%)	298 (42%)	344 (48%)	71 (10%)	713 (100%)	707 (99%)	6 (0.8%)
	clopidogrel	80	448 (62%)	204 (28%)	69 (9%)	566 (78%)	313 (43%)	297 (41%)	350 (47%)	83 (12%)	730 (100%)	726 (99.5%)	4 (0.5%)
[ISAR-REACT 5][11] Schupke et al. 2019 NEJM [NCT01944800]	ticagrelor	64.5	1534 (76.2%)	463/2011 (23.0%)	682/2002 (34.1%)	1432/2008 (71.3%)	1178/2007 (58.7%)	833 (41.4%)	930 (46.2%)	249 (12.4%)	2003 (99.6%)	1676/2009 (83.4%)	285/2009 (14.2%)
	prasugrel	64.6	1528 (76.2%)	429/2005 (21.4%)	667/1999 (33.4%)	1384/2003 (69.1%)	1163/2003 (58.1%)	820 (40.9%)	925 (46.1%)	261 (13.0%)	2001 (99.8%)	1701/2005 (84.8%)	268/2005 (13.4)
[PHILO][15] Goto et al. 2015 Circulation Journal [NCT01294462]	ticagrelor	67	306 (76.3%)	154 (38.4%)	151 (37.7%)	305 (76.1%)	314 (78.3%)	205 (51.1%)	66 (16.5%)	129 (32.2%)	385 (96.0%)	340 (84.8%)	61 (15.2%)
	clopidogrel	66	307 (76.7%)	124 (31.1%)	157 (39.3%)	290 (72.5%)	289 (72.3%)	210 (52.5%)	74 (18.5%)	116 (29.1%)	378 (95.4%)	338 (84.5%)	62 (15.5%)
[PLATO][9] Wallentin et al. 2009 NEJM [NCT00391872]	ticagrelor	62	6678 (71.6%)	2326 (24.9%)	3360 (36.0%)	6139 (65.8%)	4347 (46.6%)	3496 (37.5%)	4005 (42.9%)	1832 (19.6%)	7599 (81.4%)	5687 (60.9%)	3646 (39.1%)
	clopidogrel	62	6658 (71.7%)	2336 (25.1%)	3318 (35.7%)	6044 (65.1%)	4342 (46.7%)	3530 (38.0%)	3950 (42.5%)	1811 (19.5%)	7571 (81.5%)	5676 (61.1%)	3615 (38.9%)
[POPular AGE trial][19] Marieke 2019 [NCT02317198]	clopidogrel	77	314 (62.7%)	146 (29.1%)	NA	NA	NA	0	423 (84.6%)	78 (15.4%)	440 (87.8%)	238 (47.5%)	263 (52.5%)
	ticagrelor or prasugrel*	77	325 (64.7%)	150 (29.9)	NA	NA	NA	0	421 (83.9%)	81 (16.1%)	452 (90.0%)	245 (48.9%)	256 (51%)
[PRAGUE-18][22] Motovska et al. 2017 JACC [NCT02808767]	prasugrel	61.8	489 (77.1%)	127 (20.0%)	406 (64.0%)	326 (51.4%)	212 (33.4%)	568 (89.6%)	33 (5.2%)	33 (5.2%)	634 (100%)	629 (99.2%)	5 (0.8%)
	ticagrelor	61.8	439 (73.7%)	124 (20.8%)	392 (65.8%)	305 (51.2%)	211 (35.4%)	533 (89.4%)	34 (5.7%)	29 (4.87%)	596 (100%)	591 (99.2%)	5 (0.8%)
[The PRASFIT-ACS][19] Saito et al. 2013 Circulation Journal	prasugrel	65.4	536 (78.2%)	250 (36.5%)	273 (39.9%)	495 (72.3%)	516 (75.3%)	340 (49.6%)	187 (27.3%)	156 (22.8)	685 (100%)	NA	NA
	clopidogrel	65.1	538 (79.4%)	237 (35.0%)	279 (41.2%)	491 (72.4%)	500 (73.7%)	341 (50.3%)	213 (31.4%)	124 (18.3)	678 (100%)	NA	NA
[TICAKOREA][16] Duk-Woo Park et al. 2019 Circulation [NCT02094963]	ticagrelor	62.5	297 (74.2%)	116 (29%)	146 (36.5%)	223 (55.8%)	208 (52%)	170 (42.5%)	148 (37%)	82 (20.5%)	400 (100%)	326 (81.5%)	63 (15.8%)
	clopidogrel	62.3	302 (75.5%)	100 (25%)	139 (34.8%)	193 (48.2%)	194 (48.5%)	156 (39%)	155 (38.8%)	89 (22.2%)	400 (100%)	342 (85.5%)	52 (13%)
[TRILOGY ACS][20] Roe et al. 2012 NEJM [NCT00699998]	prasugrel	66	2835 (60.8%)	1758 (37.7%)	919 (19.7%)	3819 (81.9%)	2751 (59.0%)	0	3283 (70.4%)	1380 (29.6%)	1921 (41.2%)	0	4663 (100%)
	clopidogrel	66	2840 (60.9%)	1786 (38.3%)	942 (20.2%)	3824 (82.0%)	2765 (59.3%)	0	3236 (69.5%)	1427 (30.6%)	1930 (41.4%)	0	4663 (100%)

27

Study	Drug	Age											
[TRITON-TIMI 38][10] Wiviott et al. 2007 NEJM [NCT00097591]	prasugrel	61	5101 (75%)	1567 (23%)	2350 (38%)	4360 (64%)	3815 (56%)	1771 (26%)	5042 (74%)	0	6813 (100%)	6745 (99%)	68 (1%)
	clopidogrel	61	4960 (73%)	1563 (23%)	2582 (38%)	4349 (64%)	3805 (56%)	1767 (26%)	5028 (74%)	0	6795 (100%)	6727 (99%)	71 (1%)
Tang et al.[17] 2016 J Cardiovasc Pharmacol	ticagrelor	64.36	142 (71%)	58 (29%)	116 (58%)	122 (61%)	88 (44%)	200 (100%)	0	0	200 (100%)	200 (100%)	0 (0%)
	clopidogrel	64.18	146 (73%)	42 (21%)	124 (62%)	116 (58%)	74 (37%)	200 (100%)	0	0	200 (100%)	200 (100%)	0 (0%)
Wang et al.[18] 2016 TCRM	ticagrelor	79	69 (69%)	42 (42%)	37 (37%)	79 (79%)	84 (84%)	37 (37%)	44 (44%)	19 (19%)	86 (86%)	75 (75%)	25 (25%)
	clopidogrel	80	66 (66%)	39 (39%)	41 (41%)	82 (82%)	79 (79%)	32 (32%)	47 (47%)	21 (21%)	83 (83%)	71 (71%)	29 (29%)

* only 2% of patients received prasugrel

ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, PRASFIT-ACS – PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 – Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.
ACS – acute coronary syndrome, JACC – Journal of the American College of Cardiology, NA – not available, NEJM – The New England Journal of Medicine, NSTEMI – non-ST-elevation myocardial infarction, PCI – percutaneous coronary intervention, STEMI – ST-elevation myocardial infarction, TCRM – Therapeutics and Clinical Risk Management, UA – unstable angina

Table V. Bias assessment.

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
[The Elderly ACS II trial][21] Savonitto et al. 2018 Circulation [NCT01777503]	low	low	high	low	low	low	low
[ISAR-REACT 5][11] Schupke et al. 2019 NEJM [NCT01944800]	low	low	high	low	low	low	unclear
[PHILO][15] Goto et al. 2015 Circulation Journal [NCT01294462]	low	low	low	low	low	low	low
[PLATO][9] Wallentin et al. 2009 NEJM [NCT00391872]	low	low	low	low	low	low	low
[POPular AGE trial][14] Marieke et al. 2019 [NCT02317198]	low	low	high	low	low	low	low
[PRAGUE-18][22] Motovska et al. 2017 JACC [NCT02808767]	low	low	high	low	low	low	low
[The PRASFIT-ACS][19] Saito et al. 2013 Circulation Journal	low	unclear	low	low	low	low	low
[TICAKOREA][16] Duk-Woo Park et al. 2019 Circulation [NCT02094963]	low	low	high	low	low	low	low
[TRILOGY ACS][20] Roe et al. 2012 NEJM [NCT00699998]	low	low	low	low	low	low	low
[TRITON-TIMI 38][10] Wiviott et al. 2007 NEJM [NCT00097591]	low	low	low	low	low	low	low
Tang et al.[17] 2016 J Cardiovasc Pharmacol	low	unclear	low	unclear	low	low	low
Wang et al.[18] 2016 TCRM	low	unclear	low	unclear	low	low	low

* only 2% of patients received prasugrel

ISAR-REACT 5 – Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes, PHILO – Phase the International Study of Ticagrelor and Clinical Outcomes in Asian ACS Patients, PLATO – PLATelet inhibition and patient Outcomes, PRASFIT-ACS – PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI, TICAKOREA – Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management, TRILOGY ACS – The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, TRITON–TIMI 38 – Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38.

JACC – Journal of the American College of Cardiology, NEJM – The New England Journal of Medicine, TCRM – Therapeutics and Clinical Risk Management

Table VI. Exclusion of Trials with open-label design

All-cause mortality

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		1.06 [0.95, 1.18]	1.28 [1.15, 1.44]
Prasugrel	vs Clopidogrel	0.95 [0.85, 1.06]	vs Prasugrel	1.00	vs Ticagrelor	1.21 [1.03, 1.43]
Ticagrelor		0.78 [0.69, 0.87]		0.82 [0.70, 0.97]	1.00

Cardiovascular mortality

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		1.08 [0.95, 1.23]	1.28 [1.12, 1.47]
Prasugrel	vs Clopidogrel	0.92 [0.81, 1.05]	vs Prasugrel	1.00	vs Ticagrelor	1.18 [0.98, 1.42]
Ticagrelor		0.78 [0.68, 0.89]		0.85 [0.74, 1.02]	1.00

Non-cardiovascular mortality

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		0.97 [0.76, 1.24]	1.32 [0.92, 1.90]
Prasugrel	vs Clopidogrel	1.03 [0.81, 1.31]	vs Prasugrel	1.00	vs Ticagrelor	1.36 [0.88, 2.10]
Ticagrelor		0.76 [0.53, 1.09]		0.74 [0.48, 1.14]	1.00

Myocardial infarction

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		1.18 [0.94, 1.48]	1.16 [0.85, 1.57]
Prasugrel	vs Clopidogrel	0.85 [0.68, 1.06]	vs Prasugrel	1.00	vs Ticagrelor	0.98 [0.67, 1.44]
Ticagrelor		0.86 [0.64, 1.17]		1.02 [0.70, 1.49]	1.00

Definite or probable stent thrombosis

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		2.03 [1.52, 2.70]	1.35 [1.07, 1.71]
Prasugrel	vs Clopidogrel	0.49 [0.37, 0.66]	vs Prasugrel	1.00	vs Ticagrelor	0.67 [0.46, 0.97]
Ticagrelor		0.74 [0.59, 0.94]		1.50 [1.04, 2.17]	1.00

Stroke

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		1.08 [0.85, 1.38]	0.87 [0.68, 1.11]
Prasugrel	vs Clopidogrel	0.93 [0.73, 1.18]	vs Prasugrel	1.00	vs Ticagrelor	0.81 [0.57, 1.14]
Ticagrelor		1.15 [0.90, 1.47]		1.24 [0.88, 1.75]	1.00

Major bleeding

		HR [95% CI]			
Treatment	Comparator		Comparator		Comparator
Clopidogrel		1.00		0.79 [0.65, 0.97]	0.96 [0.87, 1.05]
Prasugrel	vs Clopidogrel	1.26 [1.04, 1.53]	vs Prasugrel	1.00	vs Ticagrelor	1.20 [0.97, 1.49]
Ticagrelor		1.05 [0.95, 1.15]		0.83 [0.67, 1.03]	1.00

*Only PLATO reported definite stent thrombosis; hence definite stent thrombosis was not estimated.