National Institute for Health and Care Excellence

Final

Acute Coronary Syndromes

[A] Evidence review for dual antiplatelet therapy

NICE guideline NG185

Intervention evidence review

November 2020

Final

This evidence review was developed by the National Guideline Centre based at the Royal College of Physicians

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1.1 Review question: Which antiplatelet is most clinically and cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults?

1.2 Introduction

The mechanism of acute coronary syndromes (ACS) involves a break in the inner (intimal) lining of the coronary arteries that exposes underlying atheroma to blood flow in the artery. When this occurs platelets in the circulating blood are stimulated causing them to aggregate, release vasoconstrictive products, and promote blood clot development. Antiplatelet drugs work by disrupting these pathways and reducing the harmful impact of platelet activation. Aspirin (ASA) blocks cyclooxygenase, an enzyme produced by platelets, and is a well-established treatment for acute coronary syndromes reducing further vascular events. Newer antiplatelet drugs have been developed that work in different ways (thienopyridine group inhibiting adenosine diphosphate pathways) and can be used in combination with aspirin to improve outcomes further.

Coronary intervention, particularly with implantation of a stent into the coronary artery, acts as a further promoter of platelet activation and benefits from more aggressive antiplatelet medication to reduce the risk of stent thrombosis. Clopidogrel was the first of the newer agents to be widely used and showed improved outcomes in comparison to aspirin alone in those with ACS at higher risk or likely to undergo percutaneous coronary intervention (PCI). However, some patients were observed to not gain maximal benefit from the combination of aspirin and clopidogrel (termed ‘clopidogrel resistance’) and newer antiplatelet drugs have been developed that have been reported to be more effective at reducing vascular events, but at the cost of higher bleeding complications.

The use of dual anti-platelet therapy, DAPT, (i.e. aspirin plus one of clopidogrel, prasugrel or ticagrelor) has therefore become accepted practice, but there has been no consensus regarding the best agent to combine with aspirin. All 3 have been assessed by NICE and are available for use in the NHS. Following the recommendation for clopidogrel in TA80, updated in CG94, TA236 recommended ticagrelor plus aspirin as an option for people with STEMI intended to be treated with primary percutaneous coronary intervention (PPCI) and for people with UA/NSTEMI. Whereas clopidogrel and ticagrelor can be used in those managed medically as well as people undergoing PCI, prasugrel is licensed only for those in whom PCI is intended, and TA317 recommended prasugrel plus aspirin as an option in this situation.

This guideline update will incorporate and contextualise the existing TA guidance by reviewing the current evidence comparing DAPT options to evaluate which is the most clinically and cost effective in people with ACS.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People with acute coronary syndromes (UA/NSTEMI and STEMI) Analysed as the overall ACS population, STEMI + revascularisation, UA/NSTEMI + revascularisation and UA/NSTEMI with no revascularisation.
Interventions	The following drug combinations will be included: • Clopidogrel + aspirin • Prasugrel + aspirin • Ticagrelor + aspirin Must be initiated as part of acute management: for example peri-procedural, or during index hospitalisation
Comparisons	Pairwise comparisons of the above dual antiplatelet therapies
Outcomes	**CRITICAL** • All-cause mortality – up to 30 days • All-cause mortality at 1 year • Cardiac mortality – up to 30 days • Cardiac mortality at 1 year • Re-infarction up to 30 days • Re- infarction at 1 year • Complications related to bleeding including haemorrhagic stroke the following hierarchy of bleeding scales will be used: ○ BARC ○ Author's definition ○ TIMI ○ GUSTO • Where possible, bleeding outcomes will be categorised into: ○ Major bleeding (including BARC 3-5 , TIMI, GUSTO and as reported by author) ○ Minor bleeding (including BARC 1-2, TIMI, GUSTO and as reported by author). • Health-related quality of life including EQ5D and SF-36 **IMPORTANT** • Stroke (any, type not specified) • Need for revascularisation • Early and late stent thrombosis • Breathing adverse effects • Bradycardic adverse effects (bradycardia, pauses and pacemaker insertion) • Other adverse effects • Unplanned urgent readmission within 30 days for any reason Where multiple timepoints are reported up to and including 30 days, only 30 day outcomes will be included. Where multiple timepoints beyond 30 days are

	reported and including up to 1 year, only up to 1 year outcomes will be reported. Where 30-day outcomes are not reported, we will include the next longest follow-up; where up to 1 year outcomes are not reported, we will include outcomes at the longest available timepoint
Study design	• Randomised Controlled Trials (RCT) • Systematic Reviews (SR) of RCTs

1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[33] Methods specific to this review question are described in the review protocol in appendix A.

Network meta-analysis (NMA) was conducted in the review, following methods described in the NMA document. The results for the NMAs informed health economic modelling and the committee's decision-making.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

1.5 Clinical evidence

1.5.1 Included studies

Twenty-eight studies (33 papers) were included in the review.[8,12,20,26,36,42,44,53,56,65,69,76,84,93,100,103,116,119,184,185,203,221,225,247,263,284,289-291,308,313,321,327] Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Alexopoulos 2012[8]	Intervention (n=28): ticagrelor + aspirin (ASA). Ticagrelor 180mg loading dose followed by 90mg bid maintenance dose starting 12±6 hours post loading dose, until day 5. All patients received oral aspirin 325mg at first medical contact. After PCI, all patients received aspirin 100mg/d indefinitely. Duration 5 days. Comparison (n=27): prasugrel + ASA. Prasugrel 60mg loading dose followed by 10mg daily maintenance dose starting 24 hours post loading dose, until day 5. All patients received oral aspirin 325mg at first medical contact. After PCI, all patients received aspirin 100mg/d indefinitely. Duration 5 days.	n=55 People with STEMI and undergoing revascularisation Age: ticagrelor group: mean 58 (SD 12); prasugrel group: mean 61 (SD 13) Male/Female ratio: 44/11 Ethnicity: not reported Greece	All-cause mortality at 5 days (at 30 days) Complications related to bleeding (major) at 5 days (at 30 days) Complications related to bleeding (minor or minimal) at 5 days (at 30 days)	Setting: Hospital Concurrent medication/care: All patients received 70 U/kg of unfractionated heparin intravenously at first medical contact and additional heparin or bivalirudin at the time of PCI per operator's discretion
Angiolillo 2016[12]	Intervention (n=51): ticagrelor + ASA. Ticagrelor 180mg loading dose after diagnostic angiography, then 90mg maintenance dose 12±1 hour after the loading	n=100 People with ACS and undergoing revascularisation	All-cause mortality at 14 days (at 30 days)	Setting: '15 US centres' Concurrent medication/care: Morphine use in catheterisation laboratory. Access site, choice of

Study	Intervention and comparison	Population	Outcomes	Comments
	dose. Study drug loading dose was administered in the catheterisation laboratory after defining coronary anatomy and before starting PCI. Afterwards, antiplatelet treatment was left to the discretion of the treating physician. All patients received a loading dose of aspirin, as per institutional standards (160-500mg), and then 75 to 100mg daily. Duration unclear. Comparison (n=49): clopidogrel + ASA. Clopidogrel 600mg loading dose after diagnostic angiography. Study drug loading dose was administered in the catheterisation laboratory after defining coronary anatomy and before starting PCI. Afterwards, antiplatelet treatment was left to the discretion of the treating physician. All patients received a loading dose of aspirin (160-500mg), as per institutional standards, and then 75 to 100mg daily. Duration unclear.	Age: ticagrelor group: mean 60.1 (SD 10.7); clopidogrel group mean: 63.0 (SD 9.1) Male/Female ratio: 70/30 Ethnicity: ticagrelor group: 71.7% white, 23.9% black or African American, 4.4% other; clopidogrel group: 71.7% white; 23.9% black or African American; 4.3% other USA	Complications related to bleeding (minor or minimal) at 14 days (at 30 days) Other adverse events at 14 days (at 30 days)	anticoagulant, stent type and procedural technique were at the physicians's discretion
Bonello 2015[20]	Intervention (n=106): ticagrelor + ASA. Ticagrelor 180mg loading dose as soon as possible after diagnosis of NSTE-ACS	n=213 People with UA/NSTEMI and undergoing revascularisation	All-cause mortality at 30 days	Setting: not reported Concurrent medication/care: All patients received their loading dose at least 4 hours before PCI

Study	Intervention and comparison	Population	Outcomes	Comments
	followed by 90mg twice daily as maintenance dose. All patients received a loading dose of 150mg aspirin IV at the time of PCI. Duration 1 month post-PCI. Comparison (n=107): prasugrel + ASA. Patients undergoing PCI received a 60mg loading dose of prasugrel as soon as the coronary anatomy was known and the decision to proceed to PCI taken. They received prasugrel 10mg daily as maintenance dose. All patients received a loading dose of 150mg aspirin IV at the time of PCI. Duration 1 month post-PCI.	Age: ticagrelor group: mean 61.5 (SD 10.4); prasugrel group: mean 60 (SD 9.6). Male/Female ratio: 159/54 Ethnicity: not reported France	Cardiac mortality (death resulting from cardiovascular disease) at 30 days Complications related to bleeding (major, BARC >2) at 30 days Stroke (any, type not specified) at 30 days	(13.4 ± 8.3 hours). PCI was performed using the radial route in all cases but 2 patients in the ticagrelor group. All patients received either a bolus of heparin (100 IU/kg) during the procedure followed by ACT-adjusted additional bolus or standard bivalirudin infusion. Drug-eluting stents were used in all patients.
Cannon 2007[26]: (DISPERSE-2)	Intervention (n=334): ticagrelor + ASA. Patients received either 90mg of ticagrelor twice daily. Patients were scheduled to receive 1, 2 or 3 months of study drug, depending on when during the trial period they were enrolled. Patients received aspirin at an initial dose of up to 325mg followed by 75 to 100mg daily. For patients undergoing PCI within 48 hours post-randomisation, an	n=661 People with UA/NSTEMI Age: ticagrelor 90 mg group: mean 64 (SD 12.1 years); ticagrelor 180mg group: mean 63 (SD 11.4); clopidogrel group: mean 62 (SD 11.0 years) based on primary safety cohort	All-cause mortality at 30 days Cardiac mortality (cardiovascular death) at 30 days Re-infarction (myocardial infarction) at 30 days Complications related to bleeding (major) at 30 days	Setting: Hospital Concurrent medication/care: Patients received standard medical (anti-ischaemic and antithrombotic) and interventional treatment for ACS, including with or without a glycoprotein IIb/IIIa inhibitor, heparin, beta-blockers and statins. Patients who received clopidogrel before randomisation were permitted in the study, but open-label clopidogrel was discontinued after

Study	Intervention and comparison	Population	Outcomes	Comments
	additional 300mg placebo could be administered at the discretion of the treating physician. Duration 4-12 weeks. Comparison (n=327): clopidogrel + ASA. Patients received 300mg clopidogrel followed by 75mg once daily. Patients were scheduled to receive 1, 2 or 3 months of study drug, depending on when during the trial period they were enrolled. Patients received aspirin at an initial dose of up to 325mg followed by 75 to 100mg daily. For patients undergoing PCI within 48 hours post-randomisation, an additional 300mg clopidogrel could be administered at the discretion of the treating physician. Duration 4-12 weeks.	Male/Female ratio: 632/352 (based on primary safety cohort) Ethnicity: ticagrelor group (90mg and 180mg groups combined): white 95%, non-white 5%; clopidogrel group: white 94%, non-white 6% Multiple countries	Complications related to bleeding (minor) at 30 days Stroke (any, type not specified) at 30 days	randomisation and replaced with study drug.
Dasbiswas 2013[36]	Intervention (n=111): prasugrel + ASA. Prasugrel loading dose of 60mg between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. Following loading dose, patients received prasugrel 10mg once daily. All patients were prescribed aspirin 325mg per day during	n=220 People with ACS and undergoing revascularisation Age: prasugrel group, mean male: 54.8 (SD 9.67); prasugrel group, mean female: 58.7 (SD 8.10); clopidogrel group, mean	All-cause mortality at 30 days Cardiac mortality at 30 days Re-infarction (non-fatal myocardial infarction) at 30 days	Setting: Hospital Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	the study. The maintenance dose was started from the next day of loading dose. Duration 12 weeks Comparison (n=109): clopidogrel + ASA. Clopidogrel loading dose of 300mg between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. Following loading dose, patients received clopidogrel 75mg once daily. All patients were prescribed aspirin 325mg per day during the study. The maintenance dose was started from the next day of loading dose. Duration 12 weeks	male: 54.6 (SD 9.65); clopidogrel group, mean female: 60.4 (SD 10.50). Male/Female ratio: not reported Ethnicity: not reported India	Complications related to bleeding (major) at 30 days Complications related to bleeding (minor) at 30 days Need for revascularisation (urgent revascularisation) at 30 days Stent thrombosis (acute) at 30 days Stroke (any, type not specified) at 30 days Other adverse effects at 30 days Unplanned urgent readmission (rehospitalisation due to cardiac arrest) at 30 days	
Dehghani 2017[44]	Intervention (n=76): ticagrelor + ASA. Ticagrelor 180mg loading dose followed by 90mg PO twice daily. Duration 30 days*. Comparison (n=68): clopidogrel + ASA.	n=144 People with STEMI and undergoing revascularisation Age: ticagrelor group mean: 62.1 (SD 10.2); clopidogrel group mean: 64.1 (SD 14.0).	All-cause mortality at 30 days Re-infarction (myocardial infarction) at 30 days Complications related to bleeding (major, BARC 3-5) at 30 days	Setting: Hospital *Concurrent medication/care: All patients received 162 to 325mg of aspirin and clopidogrel adjunctive therapy at the time of fibrinolysis as per guidelines.

Study	Intervention and comparison	Population	Outcomes	Comments
	Clopidogrel loading dose of 300mg followed by 75mg PO daily*. Duration 30 days.	Male/Female ratio: 107/37 Ethnicity: ticagrelor group: white (93.4%); clopidogrel group: white (97.1%) Canada	Complications related to bleeding (minor, BARC 1-2) at 30 days Need for revascularisation (unplanned revascularisation) at 30 days Stroke (any, type not specified) at 30 days Breathing adverse effects at 30 days Bradycardic adverse effects at 30 days Other adverse effects at 30 days Unplanned urgent readmission (rehospitalisation) at 30 days	
Goto 2015[53]: PHILO trial	Intervention (n=401): ticagrelor + ASA. Ticagrelor. An initial loading dose of 180mg ticagrelor, followed by 90mg twice daily and once daily matching placebo tablets. In patients undergoing CABG, the blinded study drug (eg. active drug or	n=801 People with ACS and undergoing revascularisation Age: ticagrelor group: mean 67 (SD 12); clopidogrel group: mean 66 (SD 11).	All-cause mortality at 1 year Cardiac mortality (including cardiovascular/vascular) at 1 year Re-infarction (myocardial infarction excluding silent	Setting: Hospital Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	placebo) was withheld for 24-72 hours in the ticagrelor group. All patients received aspirin at a dose of 75-100mg once daily (a loading dose of up to 330mg was permitted) unless aspirin was contraindicated or poorly tolerated. Duration 12 months. Comparison (n=400): clopidogrel + ASA. Patients who were clopidogrel naive received an initial loading dose of 300mg clopidogrel orally or matching placebo, then 75mg once daily and placebo capsules twice daily thereafter. Patients in the clopidogrel group who had already received a loading dose or who were already taking maintenance doses of clopidogrel or ticlopidine for ≥5 days prior to randomisation were given clopidogrel 75mg once daily plus placebo capsules twice daily. All patients received aspirin at a dose of 75-100mg once daily (a loading dose of up to 330mg was permitted) unless aspirin was contraindicated or poorly tolerated. Duration 12 months.	Male/Female ratio: ticagrelor group: 306/95; clopidogrel group: 302/98 Ethnicity: Asian (Chinese, Japanese, Korean and unknown ethnic groups) Multiple countries	myocardial infarction) at 1 year Complications related to bleeding (major) at 1 year Complications related to bleeding (minor) at 1 year Stroke (any, type not specified) at 1 year Breathing adverse effects at 1 year Bradycardic adverse effects at 1 year Other adverse effects at 1 year	

Study	Intervention and comparison	Population	Outcomes	Comments
Han 2019[56]	Intervention (n=60): ticagrelor + ASA. Ticagrelor loading dose of 180mg and 300mg of aspirin. After PCI, patients took 90mg of ticagrelor, twice a day. Patients also orally took 100mg of aspirin once a day. Duration 12 months. Comparison (n=60): clopidogrel + ASA. Clopidogrel load dose of 600mg and 300mg of aspirin. After PCI, patients took 75mg of clopidogrel once a day. Patients also orally took 100mg of aspirin once a day. Duration 12 months.	n=120 People with STEMI undergoing emergency PCI Age – mean (SD): ticagrelor group: 67 (8); clopidogrel group: 67 (8) years Male/Female ratio: 65/56 Ethnicity: not reported China	Cardiac mortality at 30 days Re-infarction at 30 days Complications related to bleeding (major) at 30 days Complications related to bleeding (minor) at 30 days	Setting: Hospital Concurrent medication/care: not reported
Jing 2016[65]	Intervention (n=94): ticagrelor + ASA. Ticagrelor loading dose of 180mg and 300mg aspirin. After the primary PCI, 90mg ticagrelor was used daily for at least 12 months. Aspirin 100mg daily was used indefinitely. Duration Not reported. Comparison (n=94): clopidogrel + ASA. Loading dose of 600mg clopidogrel and 300mg aspirin. After the primary PCI, a	n=188 People with STEMI and undergoing revascularisation Age: Clopidogrel group: 55 (16); ticagrelor group: 59 (21) Male/Female ratio: 112/76 Ethnicity: Chinese China	All-cause mortality in-hospital (up to 30 days) Cardiac mortality in-hospital (up to 30 days) Complications related to bleeding (life threatening or intracranial haemorrhage) in-hospital (up to 30 days) Complications related to bleeding (mild) in-hospital (up to 30 days)	Setting: Hospital Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	maintenance dose of 75mg clopidogrel was used daily for at least 12 months. Aspirin 100mg daily was used indefinitely. Duration Not reported			
Kitano 2019[76]	Intervention (n=39): prasugrel + ASA. Prasugrel loading dose of 20mg and 162mg of aspirin. After primary PCI, patients were given 3.75 mg of prasugrel once a day and 100mg once a day or aspirin. Duration 8 months. Comparison (n=39): clopidogrel + ASA. Clopidogrel loading dose of 75 mg once a day and 100mg once a day. After primary PCI, patients were 75mg clopidogrel once a day and 100mg of aspirin once a day. Duration 8 months.	n=78 People with ACS (STEMI, NSTEMI and unstable angina) Age: prasugrel group: 66 (13); clopidogrel group: 64 (11) Male/Female ratio: 64/14 Ethnicity: not reported Japan	All-cause mortality at 1 year Stroke (any, type not specified) at 1 year Need for revascularisation at 1 year	Setting: Hospital Concurrent medication/care: not reported
Laine 2014[84]	Intervention (n=50): ticagrelor + ASA. Patients in both groups received a 250mg intravenous loading dose of aspirin on admission followed by 75mg per dose daily indefinitely. After randomisation, patients	n=100 People with UA and undergoing revascularisation Age: ticagrelor group: 64.8 (8.9); prasugrel group: 62.8 (8.2)	All-cause mortality in-hospital (up to 30 days) Cardiac mortality in-hospital (up to 30 days) Re-infarction in-hospital (up to 30 days)	Setting: Hospital Concurrent medication/care: Glycoprotein 2b/3a inhibitors were not used, and all patients received a 4,000 UI bolus of heparin intravenously during PCI.

Study	Intervention and comparison	Population	Outcomes	Comments
	received 180mg ticagrelor as a loading dose. The maintenance dose of ticagrelor was 90mg twice daily. Duration Unclear duration of follow-up. Comparison (n=50): prasugrel + ASA. Patients in both groups received a 250mg intravenous loading dose of aspirin on admission followed by 75mg per dose daily indefinitely. After randomisation, patients received 60mg prasugrel as a loading dose. The maintenance dose of prasugrel was 10mg daily. Duration Unclear duration of follow-up.	Male/Female ratio: 76/24 Ethnicity: not reported France	Complications related to bleeding (major, BARC >3) in-hospital (up to 30 days) Stroke (any, type not specified) in-hospital (up to 30 days)	
Lee 2015[93]	Intervention (n=20): ticagrelor + ASA. Ticagrelor loading dose of 180mg in combination with 300mg aspirin in the emergency room prior to arrival at the cardiac catheterisation room. Ticagrelor 90mg twice daily was administered continuously during the follow-up as the maintenance dose. Duration 30 days. Comparison (n=19): prasugrel + ASA.	n=39 People with STEMI and undergoing revascularisation Age: ticagrelor group: mean 55 (SD 11); prasugrel group: mean 55 (SD 10) Male/Female ratio: 35/4 Ethnicity: Korean South Korea	Other adverse effects at 30 days	Setting: Hospital Concurrent medication/care: Glycoprotein IIb/IIIa inhibitors intracoronary only were permitted for use at the discretion of the attending physician.

Study	Intervention and comparison	Population	Outcomes	Comments
	Prasugrel loading dose of 60mg in combination with 300mg aspirin in the emergency room prior to arrival at the cardiac catheterisation room. Prasugrel 10mg 4 times daily was administered continuously during the follow-up as the maintenance dose. Duration 30 days.			
Li 2018[100]	Intervention (n=329): ticagrelor + ASA. Ticagrelor loading dose of 180mg ticagrelor in combination with 300mg loading dose of aspirin. After primary PCI, patients received 90mg twice a day along with 100 mg aspirin daily, as a maintanence dose. Duration 12 months. Comparison (n=324): clopidogrel + ASA. Clopidogel loading dose of 600mg in combination with 300mg of aspirin. After primary PCI, patients received 75mg once daily along with 100mg aspirin daily, as a maintenance dose. Duration 12 months.	n=653 People with STEMI undergoing primary PCI Age – mean (SD): ticagrelor group: 60 (11); clopidogrel group: 63 (13) Male/Female ratio: 346/96 Ethnicity: not reported China	Re-infarction at 1 year Cardiac mortality at 1 year Stroke (ischemic) at 1 year Complications related to bleeding (major, BARC – 3a and 3b) at 1 year Complications related to bleeding (minor, BARC = 1) bleeding at 1 year Need for revascularisation at 1 year Stent thrombosis at 1 year	Setting: Hospital Concurrent medication/care: Other drugs (i.e. beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker and proton pump inhibitor) decisions were made by the treating physicians
Motovska 2016[119]: PRAGUE-18	Intervention (n=596): ticagrelor + ASA.	n=1230	All-cause mortality at 30 days	Setting: Hospital

Study	Intervention and comparison	Population	Outcomes	Comments
	Ticagrelor 180mg loading dose and 90mg twice daily as a maintenance dose. Administration of the loading dose was recommended immediately after the patients signed the informed consent. In individual cases in which the physician could not exclude the need for urgent surgical revascularisation on the basis of previous assessments or in cases involving haemodynamic instability, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI. The decision to perform the procedure was left to the discretion of the treating physician. Patients were advised to use the study medication for 12 months. Use of aspirin was also required with a recommendation of 100mg daily. Duration 30 days. Comparison (n=634): prasugrel + ASA. Prasugrel 60mg loading dose and 10mg once daily as a maintenance dose. In patients aged >75 years of age or in those with a weight <60kg, the maintenance dose of prasugrel was reduced to 5mg once daily.	People with ACS with or without revascularisation Age: ticagrelor group: 61.8 (44.6-79.8); prasugrel group: 61.8 (42.7-78.7) Male/Female ratio: 928/302 Ethnicity: not reported Czech Republic	Cardiac mortality (death resulting from cardiovascular disease) at 30 days Re-infarction at 30 days Complications related to bleeding (major, BARC 3 or 5) at 30 days Complications related to bleeding (minor, BARC 1-2) at 30 days Stent thrombosis (definite) at 30 days	Concurrent medication/care: The decision to administer any adjunctive medication to support PCI was left to the discretion of the treating physician.

Study	Intervention and comparison	Population	Outcomes	Comments
	Administration of the loading dose was recommended immediately after the patients signed the informed consent. In individual cases in which the physician could not exclude the need for urgent surgical revascularisation on the basis of previous assessments or in cases involving haemodynamic instability, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI. In cases in which primary PCI was not performed, prasugrel therapy was discontinued and replaced by clopidogrel. The decision to perform the procedure was left to the discretion of the treating physician. Patients were advised to use the study medication for 12 months. Use of aspirin was also required with a recommendation of 100mg daily. Duration 30 days.			
Parodi 2013[185]: RAPID	Intervention (n=25): ticagrelor + ASA. Ticagrelor 180mg loading dose before PPCI. The loading dose was performed as soon as possible in the Emergency Room or in the Cath Lab. Dual antiplatelet therapy (100mg aspirin associated with 180mg	n=50 People with STEMI undergoing revascularisation Age: ticagrelor group: mean 67 (SD 10); prasugrel group: mean 67 (SD 14)	All-cause mortality in-hospital (up to 30 days) Re-infarction (myocardial infarction) in-hospital (up to 30 days)	Setting: Hospital Concurrent medication/care: Bivalirudin: bolus 0.75mg/kg followed by 1.75mg/kg/h infusion during PCI, after PPCI a bivalirudin infusion of 0.25mg/kg/h for 4 hours was allowed; unfractionated heparin use was

Study	Intervention and comparison	Population	Outcomes	Comments
	prasugrel) was recommended for 12 months, with a loading dose of 500mg of aspirin followed by 100mg daily dose. Duration Unclear. Comparison (n=25): prasugrel + ASA. Prasugrel 60mg loading dose before PPCI. The loading dose was performed as soon as possible in the Emergency Room or in the Cath Lab. Dual antiplatelet therapy (100mg aspirin associated with 5 or 10mg prasugrel) was recommended for 12 months, with a loading dose of 500mg of aspirin followed by 100mg daily dose. Duration Unclear.	Male/Female ratio: 39/11 Ethnicity: not reported Italy	Complications related to bleeding (major, TIMI) in-hospital (up to 30 days) Stroke in-hospital (up to 30 days) Complications related to bleeding (minor, TIMI) in-hospital (up to 30 days) Stent thrombosis in-hospital (up to 30 days) Bradycardiac adverse effects in-hospital (up to 30 days) Other adverse effects in-hospital (up to 30 days)	discouraged; and glycoprotein IIb/IIIa inhibitors were not allowed.
Parodi 2014[184]: RAPID 2	Intervention (n=25): ticagrelor + ASA. A loading dose of 500mg intravenous aspirin was administered in the ambulance or at the patient's home followed by 100mg daily dose. A 360mg loading dose of ticagrelor was given before PPCI. The loading dose of ticagrelor was performed as soon as possible in the emergency department or in the catheterisation laboratory. Dual antiplatelet therapy (100mg aspirin associated with	n=50 People with STEMI undergoing revascularisation Age: ticagrelor group: mean 63 (SD 11); prasugrel group: mean 67 (SD 12) Male/Female ratio: 32/18 Ethnicity: not reported Italy	All-cause mortality at 12 hours (up to 30 days) Re-infarction at 12 hours (up to 30 days) Complications related to bleeding (major, TIMI) at 12 hours (up to 30 days) Complications related to bleeding (minor, TIMI at 12 hours (up to 30 days)	Setting: Emergency department (with prior administration of aspirin in ambulance or at patient's home) Concurrent medication/care: Bivalirudin: bolus of 0.75mg/kg followed by 1.75mg (kg h) infusion during PPCI. After PPCI, a bivalirudin infusion of 0.25mg (kg h) for 4 hours was performed in all the patients. Unfractionated heparin use was discouraged. Glycoprotein IIb/IIIa inhibitors were not allowed.

Study	Intervention and comparison	Population	Outcomes	Comments
	180mg ticagrelor) was recommended for 12 months. Duration 12 months. Comparison (n=25): prasugrel + ASA. A loading dose of 500mg intravenous aspirin was administered in the ambulance or at the patient's home followed by 100mg daily dose. A 60mg loading dose of prasugrel was given before PPCI. The loading dose of prasugrel was performed as soon as possible in the emergency department or in the catheterisation laboratory. Dual antiplatelet therapy (100mg aspirin associated with 5 or 10mg prasugrel) was recommended for 12 months. Duration 12 hours.		Stent thrombosis (acute; type not specified) at 12 hours (up to 30 days) Stroke (any, type not specified) at 12 hours (up to 30 days) Bradycardic adverse effects at 12 hours (up to 30 days) Other adverse effects at 12 hours (up to 30 days)	
Roe 2012[203]; Kaul 2016[69]:TRILOGY*	Intervention (n=4663): prasugrel + ASA. Patients who underwent randomisation within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30mg of prasugrel, which was followed by daily blinded maintenance administration of a study drug. Patients who did not undergo randomisation within 72 hours	n=9326 People with UA/NSTEMI and not undergoing revascularisation Age: prasugrel group: median 66 (IQR 58-74); clopidogrel group: median 66 (IQR 59-73).	All-cause mortality up to 30 days Cardiac mortality (cardiovascular death in people aged <75 years) up to 1 year Cardiac mortality (cardiovascular death) up to 30 days	Setting: Hospital Concurrent medication/care: Not reported in study methods but the majority of patients received concomitant beta-blocker, ACE inhibitor or angiotensin-receptor blocker and statin at randomisation. Angiography was performed before randomisation in 41.2% of the prasugrel group; angiography was performed

Study	Intervention and comparison	Population	Outcomes	Comments
	were required to be treated with open-label clopidogrel before randomisation and were started on daily maintenance administration of a study drug after randomisation. The prasugrel maintenance dose was 10mg, which was adjusted to 5mg for patients who were 75 years of age or older or who weighed less than 60kg. Concomitant treatment with aspirin was required, and a daily dose of 100mg or less was strongly recommended. Duration 30 months. Comparison (n=4663): clopidogrel + ASA. Patients who underwent randomisation within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 300mg of clopidogrel, which was followed by daily blinded maintenance administration of a study drug. Patients who did not undergo randomisation within 72 hours were required to be treated with open-label clopidogrel before randomisation and were started on daily maintenance administration of a study drug after randomisation. The	Male/Female ratio: prasugrel group: 2835/1828; clopidogrel group: 2840/1823 Ethnicity: not reported Multiple countries	Re-infarction (myocardial infarction in people aged <75 years) up to 1 year Re-infarction (myocardial infarction) up to 30 days Complications related to bleeding (major, TIMI) up to 30 days Complications related to bleeding (minor, TIMI) up to 30 days Health-related quality of life (EQ5D in people aged <75 years) at 1 year Health-related quality of life (SAQ Physical in people aged <75 years) at 1 year Health-related quality of life (SF-12 Physical in people aged <75 years) at 1 year Health-related quality of life (SF-12 Mental in people aged <75 years) at 1 year Health-related quality of life (SF-36 Mental in people aged <75 years) at 1 year	before randomisation in 41.4% of the clopidogrel group. *30 day outcome data was requested and received from authors

Study	Intervention and comparison	Population	Outcomes	Comments
	clopidogrel maintenance dose was 75mg for all patients. Concomitant treatment with aspirin was required, and a daily dose of 100mg or less was strongly recommended. Duration 30 months.		Stroke (any, type not specified in people aged <75 years) up to 1 year Stroke (any, type not specified) up to 30 days	
Savonitto 2018[221]	Intervention (n=720): prasugrel +ASA. Prasugrel 60mg loading dose followed by 5mg once daily. In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI (eg. on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomisation was to take place after angiography, and the loading dose should be administered either	n=1455 People with ACS and undergoing revascularisation Age: median 80 (IQR 77-84 years). Male/Female ratio: 867/576 Ethnicity: not reported Italy	All-cause mortality at 1 year Cardiac mortality (cardiovascular death) at 1 year Re-infarction (myocardial infarction) at 1 year Complications related to bleeding (major, BARC 3 or 5) at 1 year Complications related to bleeding (minor, BARC 2) at 1 year Stent thrombosis (probable, or definite) at 1 year Stroke (any, type not specified) at 1 year	Setting: Hospital Concurrent medication/care: Proton pump inhibitors were recommended in all patients throughout the study. The selection of periprocedural anticoagulants and glycoprotein IIb/IIIa receptor blockers was left to the investigators' discretion. Whereas the use of oral anticoagulants at the time of the index event was a contraindication to enrollment in the study, their subsequent use for conditions that could have developed during follow-up (eg. atrial fibrillation) was left to the discretion of the attending physician as clinically indicated.

Study	Intervention and comparison	Population	Outcomes	Comments
	immediately before PCI or on arrival in the coronary care unit. Ongoing clopidogrel treatment, either preexisting or started as soon as the diagnosis of NSTE-ACS was made (with a loading dose of 300 or 600mg left to the investigators' discretion), did not preclude enrollment. In this case, those randomised to prasugrel received a 30mg loading dose immediately after randomisation. All patients were to receive 325mg aspirin on admission and then 75 to 100mg daily throughout follow-up. Duration 12 months. Comparison (n=735): clopidogrel + ASA. Clopidogrel 300-600mg loading dose (at investigators' discretion) followed by 75mg once daily. In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI ((eg. on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated		Other adverse effects at 1 year Unplanned urgent readmission (rehospitalisation for cardiovascular causes or bleeding) at 1 year	

Study	Intervention and comparison	Population	Outcomes	Comments
	with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomisation was to take place after angiography, and the loading dose should be administered either immediately before PCI or on arrival in the coronary care unit. Ongoing clopidogrel treatment, either preexisting or started as soon as the diagnosis of NSTE-ACS was made (with a loading dose of 300 or 600mg left to the investigators' discretion), did not preclude enrollment. In this case, those randomised to clopidogrel were to continue clopidogrel 75mg daily without a further loading dose. All patients were to receive 325mg aspirin on admission and then 75 to 100mg daily throughout follow-up. Duration 12 months.			
Schüpke 2019[225] ISAR-REACT 5	Intervention (n=2012): Ticagrelor + ASA. Loading dose of ticagrelor, 180 mg and continued at a maintenance dose of 90 mg twice daily. At discharge 94.5% of patients had aspirin (100mg or less). Duration 12 months.	n=4018 People with acute coronary syndrome for which invasive evaluation was planned (i.e., the patient was scheduled to undergo coronary angiography)	All-cause mortality at 1 year Cardiac mortality at 1 year Re-infarction at 1 year Stroke at 1 year	Setting: Hospitals and cardiac centres (multicentre trial) Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	Comparison (n=2006): Prasugrel + ASA. Loading dose of prasugrel, 60 mg and continued at a maintenance dose of 10 mg once per day. At discharge 94.5% of patients had aspirin (100mg or less). Duration 12 months.	STEMI –41.2% UA/NSTEMI –46.1% Unstable angina – 12.7% PCI – 84.1% of participants Age: Ticagrelor group: 64.5 (12) years; Prasugrel group: 64.6 (12.1) years Male/Female ratio: 3062/956 Ethnicitiy: not reported Germany and Italy	Stent thrombosis (definite or probable) at 1 year Major bleeding (major, BARC 3,4 or 5) at 1 year	
Tang 2016[263]	Intervention (n=210): ticagrelor + ASA. Patients received 300mg of aspirin and a loading dose of 180mg ticagrelor before PPCI. After PPCI, the patients were given 100mg of aspirin daily and 90mg of ticagrelor twice daily. Duration 6 months. Comparison (n=210): clopidogrel + ASA. Patients received 300mg of aspirin and a loading dose of 600mg of clopidogrel before PPCI. After PPCI, the patients were given 100mg of aspirin daily and 75mg of clopidogrel once daily. Duration 6 months.	n=420 People with STEMI and undergoing revascularisation Age: ticagrelor group: mean 64.36 (SD 11.409); clopidogrel group: mean 64.18 (SD 11.088). Male/Female ratio: 288/112 Ethnicity: not reported China	All-cause mortality at 6 months Cardiac mortality (cardiovascular cause) at 6 months Re-infarction (non-fatal myocardial infarction) at 6 months Complications related to bleeding (major, TIMI) at 6 months Complications related to bleeding (minor, TIMI) at 6 months	Setting: All patients were hospitalised in the cardiac intensive care unit. During the 6-month follow-up, the data were recorded via telephone interviews or outpatient follow-up visits Concurrent medication/care: All patients without any contraindication also received conventional drugs, such as β-blockers, angiotensin-converting enzymes/angiotensin receptor blockers, and statins in accordance with the 2013 ACCF/AHA guideline for the management of STEMI: a report of the American College of Cardiology Foundation/American Heart Association Task Force on

Study	Intervention and comparison	Population	Outcomes	Comments
			Need for revascularisation (unplanned revascularisation) at 6 months Stent thrombosis at 6 months Stroke (any, type not specified) at 6 months	Practice Guidelines. Some patients were treated with GPIIb/IIIa inhibitors [intracoronary bolus of tirofiban (10µg/kg) plus maintenance infusion (0.15µg-1.kg-1.min-1) for 24-36 hours] in accordance with the 2014 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation. The doctors who performed coronary angiography decided whether clopidogrel or ticagrelor treatments were supplemented with GPIIb/IIIa inhibitors after coronary angiography, but the doctors were blinded regarding the groups to which the patients belonged.
Wallentin 2009[284]; Lindholm 2014[103]; Steg 2010[247] (PLATO)*	Intervention (n=9333): ticagrelor + ASA. Ticagrelor loading dose of 180mg followed by a dose of 90mg twice daily. Patients undergoing PCI after randomisation received, in a blind fashion, an additional dose of ticagrelor at the time of PCI: 90mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomisation. In patients undergoing CABG, it was recommended that the study	n=18,624 People with ACS with or without revascularisation Age: ticagrelor group median: 62 (IQR or range not reported); clopidogrel group median: 62 (IQR or range not reported) Male/Female ratio: 13336/5288	All-cause mortality at 30 days All-cause mortality up to 1 year Cardiac mortality (death from including vascular causes and unknown deaths) at 30 days Cardiac mortality (death from vascular causes) at 1 year	Setting: Multicentre trial Concurrent medication/care: All patients received acetylsalicyclic acid (aspirin) at a dose of 75 to 100mg daily unless they could not tolerate the drug. For those who had not been receiving aspirin, 325mg was the preferred loading dose; 325mg was also permitted as the daily dose for 6 months after stent placement.

Study	Intervention and comparison	Population	Outcomes	Comments
	drug be withheld - in the ticagrelor group, for 24 to 72 hours. Duration 12 months. Comparison (n=9291): clopidogrel + ASA. Patients in the clopidogrel group who had not received an open-label loading dose and had not been taking clopidogrel for at least 5 days before randomisation received a 300-mg loading dose followed by a dose of 75mg daily. Others in the clopidogrel group continued to receive a maintenance dose of 75mg daily. Patients undergoing PCI after randomisation received, in a blind fashion, an additional dose of clopidogrel at the time of PCI: 300mg of clopidogrel, at the investigator's discretion. In patients undergoing CABG, it was recommended that the study drug be withheld - in the clopidogrel group, for 5 days. Duration 12 months.	Ethnicity: ticagrelor group: white (91.8%), black (1.2%), asian (5.8%), other (1.2%); clopidogrel group: white (91.6%), black (1.2%), asian (6.0%), other (1.2%) Multiple countries	Cardiac mortality (cardiovascular death including vascular and unknown deaths) up to 1 year Re-infarction at 30 days Re-infarction up to 1 year Complications related to bleeding (major) at 30 days Complications related to bleeding (major) at 1 year Complications related to bleeding (minor) at 1 year Stent thrombosis (definite) at 1 year Stent thrombosis (probable or definite) at 1 year Stent thrombosis (possible, probable or definite) at 1 year Stroke (any, type not specified) at 30 days	*30 day outcome data was requested and received from authors

Study	Intervention and comparison	Population	Outcomes	Comments
			Stroke (any, type not specified) up to 1 year Breathing adverse effects up to 1 year Bradycardic adverse effects at 30 days Bradycardic adverse effects at 1 year Other adverse effects up to 1 year	
Wang 2016a[289]	Intervention (n=100): ticagrelor + ASA. Ticagrelor 180mg loading dose, and then a maintenance dose of 90mg twice daily. The initial loading dose was administered as soon as possible after randomisation with the first maintenance dose administered at the usual time. All patients took aspirin at a loading dose of 300mg followed by a maintenance dose of 100mg once daily, unless aspirin was intolerant. Duration 12 months. Comparison (n=100): clopidogrel +ASA.	n=200 People with ACS with or without revascularisation Age: median (range): 79 (65-93) Male/Female ratio: ticagrelor group: 69/31; clopidogrel group: 66/33; Ethnicity: Chinese China	All-cause mortality up to1 year Cardiac mortality (cardiovascular death) up to 1 year Re-infarction (myocardial infarction) up to1 year Complications related to bleeding (major) up to 1 year Complications related to bleeding (minor) up to 1 year Stroke (any, type not specified) up to 1 year	Setting: not reported Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	Clopidogrel 300mg loading dose with a maintenance dose of 75mg once daily. The initial loading dose was administered as soon as possible after randomisation with the first maintenance dose administered at the usual time. All patients took aspirin at a loading dose of 300mg followed by a maintenance dose of 100mg once daily, unless aspirin was intolerant. Duration 12 months.			
Wang 2016b[290]	Intervention (n=87): ticagrelor + ASA. Ticagrelor loading dose of 180mg and then switched to an oral maintenance dose of 90mg twice daily. Duration 30 days. Comparison (n=87): clopidogrel + ASA. Clopidogrel loading dose of 600mg and then switched to an oral maintenance dose of 75mg daily. Duration 30 days.	n=174 People with STEMI and undergoing revascularisation Age: range: 60-79 Male/Female ratio: ticagrelor group: 48/39; clopidogrel group: 50/37 Ethnicity: not reported China	Cardiac mortality (vascular cause of death) at 30 days Re-infarction (recurrent myocardial infarction) at 30 days Stent thrombosis at 30 days Stroke (any, type not specified) at 30 days Breathing adverse effects at 30 days Bradycardic adverse effects at 30 days	Setting: Hospital Concurrent medication/care: If patients were not already taking aspirin, they received aspirin at a loading dose of 300mg. After the loading dose of aspirin, patients immediately underwent coronary arteriography and PCI.

Study	Intervention and comparison	Population	Outcomes	Comments
			Other adverse effects at 30 days	
Wang 2019[291]	Intervention (n=150): ticagrelor + ASA. Ticagrelor loading dose of 180mg with aspirin. After primary PCI, patients received ticagrelor at 90mg twice daily. Duration not reported. Comparison (n=148): clopidogrel + ASA. Clopidogrel loading dose of 600mg with aspirin. After primary PCI, patients received clopidogrel at 75mg daily. Duration not reported.	n=298 People with STEMI who underwent PCI Age - mean (SD): ticagrelor group: 60 (13); clopidogrel group: 61 (12) Male/Female ratio: 236/62 Ethnicity: not reported China	All-cause mortality at 30 days and 6 months (up to 1 year) Re-infarction at 30 days and 6 months (up to 1 year) Need to revascularisation at 30 days and 6 months (up to 1 year) Complications relating to bleeding (major, TIMI) during hospitalisation (up to 30 days) Complications relating to bleeding (minor, TIMI) during hospitalisation (up to 30 days)	Setting: Hospital Concurrent medication/care: All patients were managed in the cardiac care unit to receive standard pharmacological treatment, including aspirin, clopidogrel, ticagrelor, β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, unless contraindicated
Wiviott 2007[308]; De Servi 2014[42]; Montalescot 2009[116] (TRITON)	Intervention (n=6813): prasugrel + ASA. Prasugrel loading dose of 60mg administered anytime between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. If the coronary anatomy was	n=13,608 People with ACS and undergoing revascularisation Age: prasugrel group median (25th percentile, 75th	All-cause mortality at 15 months (up to 1 year) Cardiac mortality (cardiovascular death) at 30 days	Setting: Hospital Concurrent medication/care: The choice of vessels treated, devices used, and adjunctive medication administered to support PCI was left to the discretion of the treating physician.

Study	Intervention and comparison	Population	Outcomes	Comments
	previously known or primary PCI for ST-elevation myocardial infarction was planned, pretreatment with the study drug was permitted for up to 24 hours before PCI. After PCI, patients received a maintenance dose of 10mg prasugrel daily. Use of aspirin was required, and a daily dose of 75 to 162mg was recommended. Duration 15 months. Comparison (n=6795): clopidogrel + ASA. Clopidogrel loading dose of 300mg administered anytime between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. If the coronary anatomy was previously known or primary PCI for ST-elevation myocardial infarction was planned, pretreatment with the study drug was permitted for up to 24 hours before PCI. After PCI, patients received a maintenance dose of 75mg clopidogrel daily. Use of aspirin was required, and a daily dose of 75 to 162mg was recommended. Duration 15 months.	percentile): 61 (53-69); clopidogrel group median (25th percentile, 75th percentile): 61 (53-70). Male/Female ratio: prasugrel group: 5110/1703; clopidogrel group: 4960/1835 Ethnicity: prasugrel group: white 92%, non-white 8%; clopidogrel group: white 93%, non-white 7 % Multiple countries	Cardiac mortality (death from cardiovascular causes) at 15 months (up to 1 year) Re-infarction (myocardial infarction) at 30 days Re-infarction (non-fatal or all myocardial infarctions (TRITON)) at 15 months (up to 1 year) Re-infarction (myocardial infarction) at 15 months (up to 1 year) Complications related to bleeding (non-CABG related major, TIMI) at 30 days Complications related to bleeding (CABG-related major, TIMI) at 15 months (up to 1 year) Complications related to bleeding (non-CABG-related major, TIMI) at 15 months Complications related to bleeding (non-CABG-related, minor, TIMI) at 30 days	

Study	Intervention and comparison	Population	Outcomes	Comments
			Need for revascularisation (urgent target vessel revascularisation) at 15 months (up to 1 year) Stent thrombosis at 30 days Stent thrombosis (probable or definite) at 15 months (up to 1 year) Stroke (any, type not specified) at 30 days Stroke (any, including non-fatal, type not specified) at 15 months (up to 1 year) Other adverse effects at 15 months (up to 1 year)	
Wu 2018[313]	Intervention (n=129): ticagrelor + ASA. Ticagrelor administered as a loading dose of 180mg with 300mg of aspirin. Patients received 90mg of ticagelor for maintenance. Duration not reported. Comparison (n=128): clopidogrel + ASA.	n=257 People being treated with acute myocardial infarction (ACS) treated within PCI. 95% - STEMI patients 5% - NSTEMI patients Age – mean (SD): ticagrelor group: 59 (10); clopidogrel group: 61 (12)	Re-infarction at 1 year Cardiac mortality at 1 year Stroke (any, type not specified) at 1 year Bradycardia at 1 year	Setting: Hospital Concurrent medication/care: not reported

Study	Intervention and comparison	Population	Outcomes	Comments
	Clopidogrel administered as a loading dose of 300mg with 300mg of aspirin. Patients received 75 mg of clopidogrel for maintenance. Duration not reported.	Male/Female ratio: 192/52 Ethnicity: not reported China	Complications related to bleeding (not specified) at 1 year Stent thrombosis at 1 year	
Yao 2017[321]	Intervention (n=60): ticagrelor + ASA. Before the emergency PCI surgery, a loading dose of ticagrelor 180 mg and aspirin 300 mg were administered orally. Duration 6 months. Comparison (n=60): clopidogrel + ASA. Before the emergency PCI surgery, a loading dose of clopidogrel 600 mg and aspirin 300 mg were administered orally. Duration 6 months.	n=120 People with ACS and undergoing revascularisation Age: 'average age of 60.2 ± 12.3' (ticagrelor group: 60.4 ± 12.7; clopidogrel group: 59.8 ± 10.8) Male/Female ratio: 74/46 Ethnicity: not reported China	All-cause mortality up to 6 months (up to 1 year) Re-infarction (second myocardial infarction) up to 6 months (up to 1 year) Complications related to bleeding (major, BARC 3-5) up to 6 months (up to 1 year) Complications related to bleeding (minor, BARC 1-2) up to 6 months (up to 1 year) Need for revascularisation (second PCI) at 6 months (up to 1 year)	Setting: Hospital Concurrent medication/care: All patients received basic treatment for AMI, including 'atorvastatin, isosorbide mononitrate, metroprolol and so forth every day. After PCI, they were all hypodermic injected with enoxaparin sodium (brand name: clexane, brought from Sanofi-Aventis Co. Ltd., licence number: H20100484 for anticoagulation'

Study	Intervention and comparison	Population	Outcomes	Comments
			Other adverse effects up to 6 months (up to 1 year)	
Zeymer 2015[327]: ETAMI trial	Intervention (n=32): prasugrel + ASA. Prasugrel loading dose of 60 mg and 8 tablets of clopidogrel placebo as early as possible. Aspirin (500 mg intravenously or 300 mg orally). Duration 30 days. Comparison (n=31): clopidogrel + ASA. Clopidogrel loading dose of 600 mg and 6 tablets of prasugrel placebo as early as possible. Aspirin (500 mg intravenously or 300 mg orally). Duration 30 days.	n=63 People with STEMI and undergoing revascularisation Age: prasugrel group: 59 (55-70); clopidogrel group: 640 (49-70) Male/Female ratio: 45/17 Ethnicity: Germany	All-cause mortality at 30 days Re-infarction at 30 days Complications related to bleeding (major or minor, TIMI) at 30 days Stent thrombosis at 30 days Other adverse effects at 30 days	Setting: In the ambulance or in the emergency department of a PCI hospital Concurrent medication/care: The administration of GP IIb/IIIa inhibitors after the diagnostic angiography and prior to or during PPCI was left to the discretion of the treating physician.

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: ticagrelor + aspirin (ASA) versus clopidogrel + aspirin (ASA)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
All-cause mortality - ACS with/without revascularisation	19812 (6 studies) 30 days	⨁⊖⊖⊖ VERY LOW[1,3] due to risk of bias, imprecision	N/A[6]	23 per 1000	4 fewer per 1000 (from 7 fewer to 0 more)
All-cause mortality - STEMI + revascularisation	630 (3 studies) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.48 (0.17 to 1.39)	32 per 1000	17 fewer per 1000 (from 27 fewer to 13 more)
All-cause mortality - UA/NSTEMI + revascularisation	6218 (1 study) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	HR 0.64 (0.44 to 0.93)	-	N/A[4]
All-cause mortality - UA/NSTEMI + no revascularisation	4514 (1 study) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	HR 0.84 (0.63 to 1.12)	-	N/A[4]
All-cause mortality - ACS with/without revascularisation	20443 (6 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.78 (0.69 to 0.88)	53 per 1000	12 fewer per 1000 (from 6 fewer to 17 fewer)
All-cause mortality - STEMI + revascularisation	8242 (3 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.8 (0.66 to 0.97)	55 per 1000	11 fewer per 1000 (from 2 fewer to 19 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
All-cause mortality - UA/NSTEMI + revascularisation	5648 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.75 (0.53 to 1.06)	-	N/A[4]
All-cause mortality - UA/NSTEMI + no revascularisation	5217 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.73 (0.57 to 0.93)	-	N/A[4]
Cardiac mortality - ACS with/without revascularisation	1143 (4 studies) 30 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.1 (0.45 to 2.69)	16 per 1000	2 more per 1000 (from 9 fewer to 27 more)
Cardiac mortality - STEMI + revascularisation	482 (3 studies) 30 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.57 (0.17 to 1.92)	29 per 1000	12 fewer per 1000 (from 24 fewer to 27 more)
Cardiac mortality - UA/NSTEMI + revascularisation	6218 (1 study) 30 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.67 (0.43 to 1.04)	-	N/A[4]
Cardiac mortality - UA/NSTEMI + no revascularisation	4514 (1 study) 30 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.84 (0.62 to 1.14)	-	N/A[4]
Cardiac mortality - ACS with/without revascularisation	20711 (6 studies) 1 year	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.78 (0.69 to 0.89)	46 per 1000	10 fewer per 1000 (from 5 fewer to 14 fewer)
Cardiac mortality - STEMI + revascularisation	8630 (4 studies) 1 year	⊕⊕⊖⊖ LOW[1,2]	RR 0.81 (0.66 to 0.98)	48 per 1000	9 fewer per 1000 (from 1 fewer to 16 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
		due to risk of bias, imprecision			
Cardiac mortality - UA/NSTEMI + revascularisation	5648 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.76 (0.52 to 1.11)	-	N/A[4]
Cardiac mortality - UA/NSTEMI + no revascularisation	5217 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.75 (0.58 to 0.97)	-	N/A[4]
Re-infarction - ACS with/without revascularisation	19818 (6 studies) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.69 (0.56 to 0.86)	20 per 1000	6 fewer per 1000 (from 3 fewer to 9 fewer)
Re-infarction - STEMI + revascularisation	736 (4 studies) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.37 (0.15 to 0.89)	47 per 1000	30 fewer per 1000 (from 5 fewer to 40 fewer)
Re-infarction - UA/NSTEMI + revascularisation	5934 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.86 (0.63 to 1.17)	-	N/A[4]
Re-infarction - UA/NSTEMI + no revascularisation	4479 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.89 (0.68 to 1.16)	-	N/A[4]
Re-infarction - ACS with/without revascularisation	21129 (8 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.83 (0.74 to 0.93)	61 per 1000	10 fewer per 1000 (from 4 fewer to 16 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Re-infarction - STEMI + revascularisation	8928 (5 studies) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.75 (0.61 to 0.91)	49 per 1000	12 fewer per 1000 (from 4 fewer to 19 fewer)
Re-infarction - UA/NSTEMI + revascularisation	5438 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.90 (0.68 to 1.19)	-	N/A[4]
Re-infarction - UA/NSTEMI + no revascularisation	5201 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.94 (0.75 to 1.18)	-	N/A[4]
Major bleeding - ACS with/without revascularisation	19832 (6 studies) 30 days	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	N/A[6]	68 per 1000	0 fewer per 1000 (from 7 fewer to 7 more)
Major bleeding - STEMI + revascularisation	750 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[6]	14 per 1000	5 more per 1000 (from 8 fewer to 43 more)
Major bleeding - UA/NSTEMI + revascularisation	4958 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.14 (0.84 to 1.55)	-	N/A[4]
Major bleeding - UA/NSTEMI + no revascularisation	3964 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.18 (0.91 to 1.53)	-	N/A[4]
Major bleeding - ACS with/without revascularisation	20206 (6 studies) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.04 (0.96 to 1.13)	96 per 1000	4 more per 1000 (from 4 fewer to 13 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Major bleeding - STEMI + revascularisation	8135 (3 studies) 1 year	⨁⨁⨀⨀ LOW[1,5] due to risk of bias, inconsistency	RR 0.96 (0.83 to 1.12)	78 per 1000	3 fewer per 1000 (from 13 fewer to 9 more)
Major bleeding - UA/NSTEMI + revascularisation	4983 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.10 (0.84 to 1.44)	-	N/A[4]
Major bleeding - UA/NSTEMI + no revascularisation	4931 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.05 (0.88 to 1.25)	-	N/A[4]
Minor bleeding - ACS with/without revascularisation	1511 (6 studies) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.49 (1.02 to 2.16)	54 per 1000	26 more per 1000 (from 1 more to 62 more)
Minor bleeding - STEMI + revascularisation	750 (4 studies) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.91 to 2.02)	97 per 1000	35 more per 1000 (from 9 fewer to 99 more)
Minor bleeding - ACS with/without revascularisation	20384 (6 studies) 1 year	⨁⨀⨀⨀ VERY LOW[1,2,5] due to risk of bias, inconsistency, imprecision	RR 1.34 (1.18 to 1.53)	37 per 1000	13 more per 1000 (from 7 more to 20 more)
Minor bleeding - STEMI + revascularisation	8313 (3 studies) 1 year	⨁⨁⨀⨀ LOW[2] due to risk of bias, imprecision	RR 1.37 (1.12 to 1.68)	37 per 1000	14 more per 1000 (from 4 more to 25 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Bleeding (type not specified) at 1 year – UA/NSTEMI with revascularisation	244 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 3.39 (1.15 to 10)	33 per 1000	80 more per 1000 (from 5 more to 300 more)
Stroke (type not specified) - ACS with/without revascularisation	19400 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[6]	5 per 1000	2 more per 1000 (from 0 fewer to 4 more)
Stroke (type not specified) - STEMI + revascularisation	318 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[6]	13 per 1000	0 fewer per 1000 (from 11 fewer to 77 more)
Stroke (type not specified) - UA/NSTEMI + revascularisation	6188 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.14 (0.54 to 2.41)	-	N/A[4]
Stroke (type not specified) - UA/NSTEMI + no revascularisation	4502 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.84 (0.50 to 1.41)	-	N/A[4]
Stroke (type not specified) - ACS with/without revascularisation	20711 (6 studies) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.13 (0.89 to 1.43)	12 per 1000	2 more per 1000 (from 1 fewer to 5 more)
Stroke (type not specified) - STEMI + revascularisation	8630 (4 studies) 1 year	⨁⨁⨀⨀ LOW[1,5] due to risk of bias, inconsistency	RR 1.29 (0.88 to 1.9)	11 per 1000	3 more per 1000 (from 1 fewer to 10 more)
Stroke (type not specified) - UA/NSTEMI + revascularisation	5632 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.18 (0.60 to 2.32)	-	N/A[4]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Stroke (type not specified) - UA/NSTEMI + no revascularisation	5209 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.92 (0.58 to 1.46)	-	N/A[4]
Need for revascularisation - STEMI + revascularisation	442 (2 studies) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	Peto OR 0.29 (0.08 to 1)	37 per 1000	26 fewer per 1000 (from 34 fewer to 0 more)
Need for revascularisation - ACS with/without revascularisation	1260 (4 studies) 1 year	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	RR 0.31 (0.16 to 0.6)	68 per 1000	47 fewer per 1000 (from 27 fewer to 57 fewer)
Need for revascularisation - STEMI + revascularisation	1140 (3 studies) 1 year	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	RR 0.27 (0.13 to 0.57)	67 per 1000	49 fewer per 1000 (from 29 fewer to 58 fewer)
Stent thrombosis (type not specified) - STEMI + revascularisation	174 (1 study) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	Peto OR 0.13 (0.02 to 0.94)	46 per 1000	40 fewer per 1000 (from 3 fewer to 45 fewer)
Stent thrombosis (probable or definite) - ACS with/without revascularisation	11289 (1 study) 1 year	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.75 (0.59 to 0.95)	28 per 1000	7 fewer per 1000 (from 1 fewer to 11 fewer)
Stent thrombosis (probable or definite) - STEMI + revascularisation	7544 (1 study) 1 year	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.73 (0.54 to 0.98)	27 per 1000	7 fewer per 1000 (from 1 fewer to 12 fewer)
Stent thrombosis (type not specified)- ACS with/without revascularisation	1086 (3 studies) 1 year	⊕⊕⊖⊖ LOW[1,3] due to risk of bias, imprecision	N/A[6]	12 per 1000	10 fewer per 1000 (from 3 fewer to 11 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Stent thrombosis (type not specified) - STEMI + revascularisation	644 (2 studies) 1 year	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[6]	9 per 1000	8 fewer per 1000 (from 9 fewer to 16 more)
Stent thrombosis (type not specified) - NSTEMI + revascularisation	442 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	Peto OR 0.21 (0.03 to 1.58)	14 per 1000	11 fewer per 1000 (from 14 fewer to 8 more)
Breathing adverse effects - STEMI + revascularisation	318 (2 studies) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 2.39 (1.09 to 5.27)	52 per 1000	72 more per 1000 (from 5 more to 220 more)
Breathing adverse effects - ACS with/without revascularisation	19222 (2 studies) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.76 (1.62 to 1.92)	76 per 1000	58 more per 1000 (from 47 more to 70 more)
Breathing adverse effects - STEMI + revascularisation	7471 (1 study) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.5 (1.31 to 1.72)	84 per 1000	42 more per 1000 (from 26 more to 60 more)
Bradycardic adverse effects - ACS with/without revascularisation	2309 (3 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.8 to 2.29)	20 per 1000	7 more per 1000 (from 4 fewer to 26 more)
Bradycardic adverse effects - STEMI + revascularisation	318 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.6 (0.62 to 4.1)	39 per 1000	23 more per 1000 (from 15 fewer to 120 more)
Bradycardic adverse effects - ACS with/without revascularisation	13632 (3 studies) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.09 (0.96 to 1.23)	47 per 1000	4 more per 1000 (from 2 fewer to 11 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Bradycardic adverse effects - STEMI + revascularisation	7715 (2 studies) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.04 (0.87 to 1.25)	56 per 1000	2 more per 1000 (from 7 fewer to 14 more)
Other adverse effects - ACS with/without revascularisation	418 (3 studies) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.26 (0.85 to 1.88)	167 per 1000	43 more per 1000 (from 25 fewer to 147 more)
Other adverse effects - STEMI + revascularisation	318 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.14 (0.70 to 1.85)	161 per 1000	23 more per 1000 (from 48 fewer to 137 more)
Other adverse effects - ACS with/without revascularisation	19342 (3 studies) 1 year	⨁⨁⨁⨀ MODERATE[1] due to risk of bias	RR 1.02 (0.94 to 1.11)	50 per 1000	1 more per 1000 (from 3 fewer to 6 more)
Other adverse effects - STEMI + revascularisation	7471 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.25 (0.9 to 1.75)	17 per 1000	4 more per 1000 (from 2 fewer to 12 more)
Unplanned urgent readmission (rehospitalisation) - STEMI + revascularisation	144 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.45 (0.08 to 2.37)	59 per 1000	32 fewer per 1000 (from 54 fewer to 81 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision
4 Absolute effects could not be calculated as event rates were not reported
5 Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis
6 No relative effect due to 0 events. Risk difference calculated in Review Manager

Table 4: Clinical evidence summary: prasugrel + aspirin (ASA) versus clopidogrel + aspirin (ASA)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
All-cause mortality - ACS with/without revascularisation	13142 (4 studies) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.56 to 1.05)	14 per 1000	3 fewer per 1000 (from 6 fewer to 1 more)
All-cause mortality - STEMI + revascularisation	3596 (2 studies) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.63 (0.40 to 1.00)	26 per 1000	9 fewer per 1000 (from 15 fewer to 0 more)
All-cause mortality – UA/NSTEMI + no revascularisation	9326 (1 study) 30 days	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 0.89 (0.58 to 1.36)	9 per 1000	1 fewer per 1000 (from 4 fewer to 3 more)
All-cause mortality - ACS with/without revascularisation	15126 (3 studies) 1 year	⊕⊕⊕⊖ MODERATE[2] due to risk of bias	RR 1 (0.83 to 1.2)	30 per 1000	0 fewer per 1000 (from 5 fewer to 6 more)
All-cause mortality - STEMI + revascularisation	3534 (1 study) 1 year	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.76 (0.54 to 1.06)	43 per 1000	10 fewer per 1000 (from 20 fewer to 3 more)
Cardiac mortality - ACS with/without revascularisation	13049 (3 studies) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.75 (0.54 to 1.05)	12 per 1000	3 fewer per 1000 (from 6 fewer to 1 more)
Cardiac mortality - STEMI + revascularisation	3534 (1 study) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of	RR 0.61 (0.37 to 1)	23 per 1000	9 fewer per 1000 (from 15 fewer to 0 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
		bias, imprecision			
Cardiac mortality – UA/NSTEMI + no revascularisation	9326 (1 study) 30 days	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.92 (0.58 to 1.46)	8 per 1000	1 fewer per 1000 (from 3 fewer to 4 more)
Cardiac mortality - ACS with/without revascularisation	15051 (2 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.88 (0.71 to 1.09)	24 per 1000	3 fewer per 1000 (from 7 fewer to 2 more)
Cardiac mortality - STEMI + revascularisation	3534 (1 study) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.74 (0.5 to 1.09)	33 per 1000	9 fewer per 1000 (from 16 fewer to 3 more)
Cardiac mortality - UA/NSTEMI + revascularisation	10074 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.98 (0.73 to 1.3)	18 per 1000	0 fewer per 1000 (from 5 fewer to 5 more)
Cardiac mortality - UA/NSTEMI + no revascularisation	9326 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 1.00 (0.78 to 1.28)	-	N/A[4]
Re-infarction - ACS with/without revascularisation	13111 (4 studies) 30 days	VERY LOW[1,3] due to risk of bias, imprecision	N/A[8]	31 per 1000	6 fewer per 1000 (from 1 fewer to 11 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
Re-infarction - STEMI + revascularisation	3596 (2 studies) 30 days	⨁⨁⨀⨀ LOW[1,3] due to risk of bias, imprecision	N/A[8]	68 per 1000	20 fewer per 1000 (from 5 fewer to 32 fewer)
Re-infarction - UA/NSTEMI + revascularisation	9326 (1 study) 30 days	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.95 (0.69 to 1.3)	17 per 1000	1 fewer per 1000 (from 5 fewer to 5 more)
Re-infarction - ACS with/without revascularisation	15051 (3 studies) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.76 (0.68 to 0.85)	87 per 1000	21 fewer per 1000 (from 13 fewer to 28 fewer)
Re-infarction - STEMI + revascularisation	3534 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.76 (0.6 to 0.95)	89 per 1000	21 fewer per 1000 (from 4 fewer to 36 fewer)
Re-infarction - UA/NSTEMI + revascularisation	10074 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.67 to 0.87)	95 per 1000	22 fewer per 1000 (from 12 fewer to 31 fewer)
Re-infarction - UA/NSTEMI + no revascularisation	9326 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	HR 0.97 (0.78 to 1.21)	-	N/A[4]
Major bleeding - ACS with/without revascularisation	12994 (3 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of	N/A[8]	4 per 1000	1 fewer per 1000 (from 2 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
		bias, imprecision			
Major bleeding - STEMI + revascularisation	3534 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.74 (0.4 to 1.38)	13 per 1000	3 fewer per 1000 (from 8 fewer to 5 more)
Major bleeding – UA/NSTEMI + no revascularisation	9240 (1 study) 30 days	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 1.17 (0.39 to 3.46)	1 per 1000	0 more per 1000 (from 1 fewer to 3 more)
Bleeding (major and minor) - STEMI + revascularisation	62 (1 study) 30 days	⨁⨁⊖⊖ LOW[1] due to imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	N/A[7]
Major bleeding - ACS with/without revascularisation	14900 (2 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.42 (1.13 to 1.77)	17 per 1000	7 more per 1000 (from 2 more to 13 more)
Major bleeding - STEMI + revascularisation	3534 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.12 (0.71 to 1.76)	19 per 1000	2 more per 1000 (from 6 fewer to 15 more)
Major bleeding - UA/NSTEMI + revascularisation	9981 (1 study) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.4 (1.05 to 1.87)	15 per 1000	6 more per 1000 (from 1 more to 13 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
Minor bleeding - ACS with/without revascularisation	3754 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2,5] due to risk of bias, inconsistency, imprecision	RR 0.69 (0.46 to 1.02)	31 per 1000	10 fewer per 1000 (from 17 fewer to 1 more)
Minor bleeding - STEMI + revascularisation	3534 (1 study) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.61 (0.4 to 0.93)	32 per 1000	13 fewer per 1000 (from 2 fewer to 19 fewer)
Minor bleeding - ACS with/without revascularisation	1443 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 2.05 (0.88 to 4.75)	11 per 1000	12 more per 1000 (from 1 fewer to 41 more)
Health-related quality of life - UA/NSTEMI + no revascularisation EQ5D. Scale from: 0 to 100.	5764 (1 study) 1 year	⨁⨁⨁⨀ MODERATE[2] due to risk of bias		The mean health-related quality of life in the control groups was 84.6	The mean health-related quality of life in the intervention groups was 1 higher (0.22 to 1.78 higher)
Health-related quality of life - UA/NSTEMI + no revascularisation SAQ Physical. Scale from: 0 to 100.	1774 (1 study) 1 year	⨁⨁⨁⨀ MODERATE[2] due to risk of bias		The mean health-related quality of life in the control groups was 77	The mean health-related quality of life in the intervention groups was 1 higher (1.17 lower to 3.17 higher)
Health-related quality of life - UA/NSTEMI + no revascularisation SF-12 Physical. Scale from: 0 to 100.	1774 (1 study) 1 year	⨁⨁⨁⨀ MODERATE[2] due to risk of bias		The mean health-related quality of life in the control groups was 43.7	The mean health-related quality of life in the intervention groups was 0.3 higher (0.7 lower to 1.3 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
Health-related quality of life - UA/NSTEMI + no revascularisation SF-12 Mental. Scale from: 0 to 100.	1774 (1 study) 1 year	⊕⊕⊕⊖ MODERATE[2] due to risk of bias		The mean health-related quality of life in the control groups was 49.7	The mean health-related quality of life in the intervention groups was 0 higher (0.97 lower to 0.97 higher)
Health-related quality of life - UA/NSTEMI + no revascularisation SF-36. Scale from: 0 to 100.	1774 (1 study) 1 year	⊕⊕⊕⊖ MODERATE[2] due to risk of bias		The mean health-related quality of life in the control groups was 47.8	The mean health-related quality of life in the intervention groups was 0.4 higher (0.64 lower to 1.44 higher)
Stroke (type not specified) - ACS with/without revascularisation	13049 (3 studies) 30 days	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.71 (0.4 to 1.27)	4 per 1000	1 fewer per 1000 (from 3 fewer to 1 more)
Stroke (type not specified) - STEMI + revascularisation	3534 (1 study) 30 days	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.44 (0.18 to 1.06)	9 per 1000	5 fewer per 1000 (from 7 fewer to 1 more)
Stroke (type not specified) – UA/NSTEMI + no revascularisation	9326 (1 study) 30 days	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 1.09 (0.48 to 2.47)	2 per 1000	0 more per 1000 (from 1 fewer to 3 more)
Stroke (type not specified) - ACS with/without revascularisation	15126 (3 studies) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.93 (0.67 to 1.29)	10 per 1000	1 fewer per 1000 (from 3 fewer to 3 more)
Stroke (type not specified) - STEMI + revascularisation	3534 (1 study) 1 year	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of	RR 1.04 (0.6 to 1.79)	14 per 1000	1 more per 1000 (from 6 fewer to 11 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
		bias, imprecision			
Stroke (type not specified) - UA/NSTEMI + revascularisation	10074 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.06 (0.71 to 1.59)	9 per 1000	1 more per 1000 (from 3 fewer to 5 more)
Stroke (type not specified) in people aged <75 years - (UA/NSTEMI + no revascularisation)	9326 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	HR 0.86 (0.50, 1.48)	-	N/A[4]
Need for revascularisation - ACS with/without revascularisation	3723 (2 studies) 30 days	⨁⨁⊖⊖ LOW[1,3] due to risk of bias, imprecision	N/A[8]	18 per 1000	6 fewer per 1000 (from 11 fewer to 2 more)
Need for revascularisation - STEMI + revascularisation	3534 (1 study) 30 days	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.67 (0.39 to 1.14)	19 per 1000	6 fewer per 1000 (from 11 fewer to 3 more)
Need for revascularisation - ACS with/without revascularisation	13683 (2 studies) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.67 (0.55 to 0.82)	34 per 1000	11 fewer per 1000 (from 6 fewer to 15 fewer)
Need for revascularisation - STEMI + revascularisation	3534 (1 study) 1 year	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.7 (0.47 to 1.06)	31 per 1000	9 fewer per 1000 (from 16 fewer to 2 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
Stent thrombosis (definite or probable) - STEMI + revascularisation	3534 (1 study) 30 days	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.49 (0.28 to 0.84)	22 per 1000	11 fewer per 1000 (from 4 fewer to 16 fewer)
Stent thrombosis (type not specified) - ACS with/without revascularisation	282 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[2,3] due to risk of bias, imprecision	N/A[8]	7 per 1000	6 fewer per 1000 (from 7 fewer to 39 more)
Stent thrombosis (type not specified) - STEMI + revascularisation	62 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	Not estimable [6]	-	N/A-[6]
Stent thrombosis (definite or probable) - ACS with/without revascularisation	15051 (2 studies) 1 year	⨁⨁⨁⨀ MODERATE[2] due to risk of bias	RR 0.47 (0.35 to 0.62)	21 per 1000	11 fewer per 1000 (from 8 fewer to 13 fewer)
Other adverse effects - ACS with/without revascularisation	282 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.7 (0.23 to 2.17)	50 per 1000	15 fewer per 1000 (from 38 fewer to 59 more)
Other adverse effects - STEMI + revascularisation	62 (1 study) 30 days	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.5 (0.05 to 5.23)	65 per 1000	32 fewer per 1000 (from 61 fewer to 273 more)
Other adverse effects - ACS with/without revascularisation	14900 (2 studies) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of	RR 1.13 (0.44 to 2.94)	10 per 1000	1 more per 1000 (from 5 fewer to 19 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clopidogrel + ASA	Risk difference with prasugrel + ASA (95% CI)
		bias, imprecision			
Unplanned urgent readmission - ACS with/without revascularisation	189 (1 study) 30 days	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.03 (0.07 to 16.26)	10 per 1000	0 more per 1000 (from 10 fewer to 159 more)
Unplanned urgent readmission - ACS with/without revascularisation	1443 (1 study) 1 year	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.77 to 1.45)	93 per 1000	5 more per 1000 (from 21 fewer to 42 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision
4 Absolute effects could not be calculated as event rates were not reported
5 Downgraded by 1 or 2 increments because heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis
6 Zero events in both arms. Relative risk and absolute effects could not be calculated.
7 Absolute effects could not be calculated due to zero events in one of the arms
8 No relative effect due to 0 events. Risk difference calculated in Review Manager

Table 5: Clinical evidence summary: ticagrelor + aspirin (ASA) versus prasugrel + aspirin (ASA)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with prasugrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
All-cause mortality - ACS with/without revascularisation	1698 (6 studies) 30 days	⨁⨁⊖⊖ LOW[3] due to imprecision	N/A[5]	22 per 1000	2 more per 1000 (from 9 fewer to 22 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with prasugrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
All-cause mortality - STEMI + revascularisation	1385 (4 studies) 30 days	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.94 (0.51 to 1.75)	28 per 1000	2 fewer per 1000 (from 14 fewer to 21 more)
All-cause mortality - UA/NSTEMI + revascularisation	313 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	6 per 1000	4 fewer per 1000 (from 6 fewer to 45 more)
All-cause mortality - ACS with/without revascularisation	4018 (1 study) 1 year	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.23 (0.9 to 1.66)	36 per 1000	8 more per 1000 (from 4 fewer to 24 more)
Cardiac mortality - ACS with/without revascularisation	1543 (3 studies) 30 days	⨁⨁⨀⨀ LOW[3] due to imprecision	N/A[5]	11 per 1000	1 fewer per 1000 (from 7 fewer to 16 more)
Cardiac mortality - STEMI + revascularisation	1230 (1 study) 30 days	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.06 (0.4 to 2.82)	13 per 1000	1 more per 1000 (from 8 fewer to 23 more)
Cardiac mortality - UA/NSTEMI + revascularisation	313 (2 studies) 30 days	⨁⨁⨀⨀ LOW[3] due to imprecision	N/A[5]	6 per 1000	4 fewer per 1000 (from 6 fewer to 45 more)
Cardiac mortality - ACS with/without revascularisation	4018 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.06 (0.75 to 1.51)	29 per 1000	2 more per 1000 (from 7 fewer to 15 more)
Re-infarction - ACS with/without revascularisation	1430 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	14 per 1000	3 fewer per 1000 (from 9 fewer to 12 more)
Re-infarction - STEMI + revascularisation	1330 (3 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	12 per 1000	1 more per 1000 (from 7 fewer to 20 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with prasugrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Re-infarction - UA/NSTEMI + revascularisation	100 (1 study) 30 days	⨁⨁⨀⨀ LOW[1] due to imprecision	Peto OR 0.14 (0.00 to 6.82)	20 per 1000	17 fewer per 1000 (from 20 fewer to 102 more)
Re-infarction - ACS with/without revascularisation	4018 (1 study) 1 year	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 1.6 (1.16 to 2.19)	30 per 1000	18 more per 1000 (from 5 more to 36 more)
Major bleeding - ACS with/without revascularisation	1698 (6 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	16 per 1000	4 fewer per 1000 (from 11 fewer to 10 more)
Major bleeding - STEMI + revascularisation	1385 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	8 per 1000	4 fewer per 1000 (from 7 fewer to 9 more)
Major bleeding - UA/NSTEMI + revascularisation	313 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	51 per 1000	6 fewer per 1000 (from 34 fewer to 69 more)
Major bleeding - ACS with/without revascularisation	3762 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.06 (0.79 to 1.42)	45 per 1000	3 more per 1000 (from 9 fewer to 19 more)
Minor bleeding - STEMI + revascularisation	1385 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.25 (0.75 to 2.09)	35 per 1000	9 more per 1000 (from 9 fewer to 38 more)
Stroke (type not specified) - ACS with/without revascularisation	1593 (4 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	4 per 1000	2 fewer per 1000 (from 3 fewer to 6 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with prasugrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Stroke (type not specified) - STEMI + revascularisation	1280 (2 studies) 30 days	⨁⨀⨀⨀ VERY LOW[1,3] due to risk of bias, imprecision	N/A[5]	3 per 1000	1 fewer per 1000 (from 3 fewer to 13 more)
Stroke (type not specified) - UA/NSTEMI + revascularisation	313 (2 studies) 30 days	⨁⨁⨀⨀ LOW[3] due to imprecision	N/A[5]	6 per 1000	5 fewer per 1000 (from 6 fewer to 36 more)
Stroke (any type) - ACS with/without revascularisation	4018 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.16 (0.62 to 2.13)	9 per 1000	2 more per 1000 (from 4 fewer to 11 more)
Need for revascularisation - STEMI + revascularisation	1230 (1 study) 30 days	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.83 (0.31 to 2.21)	14 per 1000	2 fewer per 1000 (from 10 fewer to 17 more)
Stent thrombosis (definite) - STEMI + revascularisation	1230 (1 study) 30 days	⨁⨁⨀⨀ LOW1 due to imprecision	RR 1.77 (0.43 to 7.39)	5 per 1000	4 more per 1000 (from 3 fewer to 30 more)
Stent thrombosis (type not specified) - STEMI + revascularisation	100 (2 studies) 30 days	⨁⨁⨀⨀ LOW[3] due to imprecision	N/A[5]	20 per 1000	17 fewer per 1000 (from 20 fewer to 102 more)
Stent thrombosis (definite or probable) - ACS with/without revascularisation	4018 (1 study) 1 year	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.30 (0.73 to 2.31)	10 per 1000	3 more per 1000 (from 3 fewer to 13 more)
Breathing adverse effects - STEMI + revascularisation	50 (1 study) 30 days	⨁⨁⨀⨀ LOW1 due to imprecision	Peto OR 8.83 (1.42 to 54.99)	0 per 1000	N/A[4]
Bradycardic adverse effects - STEMI + revascularisation	50 (1 study) 30 days	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 7.39 (0.15 to 372.38)	0 per 1000	N/A[4]

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with prasugrel + ASA	Risk difference with ticagrelor + ASA (95% CI)
Other adverse effects - STEMI + revascularisation	139 (3 studies) 30 days	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 1.59 (0.53 to 4.74)	58 per 1000	34 more per 1000 (from 27 fewer to 217 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
2 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
3 Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision
4 Absolute effects could not be calculated due to zero events in one of the arms
5 No relative effect due to 0 events. Risk difference calculated in Review Manager

See appendix F for full GRADE tables.

1.5.5 Network meta-analysis

The dual antiplatelets review for this guideline update (comparing asprin plus one of clopidogrel, prasugrel or ticagrelor in people with ACS) formed a connected network of RCT evidence and so an NMA was considered. This topic was considered a high clinical priority for the guideline due to variations in practice and uncertainty about the most clinically and cost effective strategy. It was also given the highest priority for new economic modelling. Given this, the committee agreed that network meta-analysis was warranted to facilitate cost effectiveness analysis and help decision making in this area. For full details behind the rationale and results, see the NMA write-up document.

Outcomes selected for the network meta-analysis

The following five outcomes were selected for the NMA:

- All-cause mortality at 30 days
- New myocardial infarction at 30 days
- Stroke at 30 days
- Major bleeding at 30 days
- Minor bleeding at 30 days

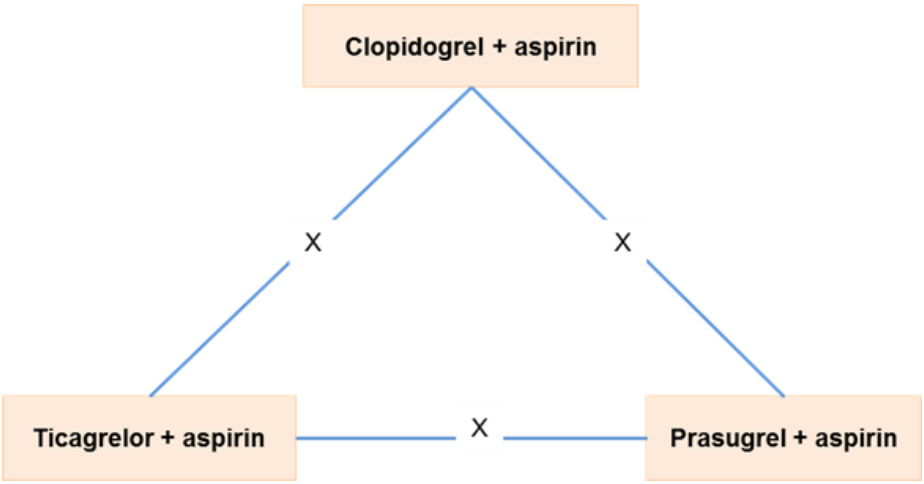
NMA of 1 year outcomes was considered but there was inconsistency in the network and so it was not considered appropriate to undertake NMA. For example, using the data for prasugrel and ticagrelor each compared to clopidogrel generated an odds ratio for ticagrelor versus prasugrel of 0.77 (0.61 to 0.97) which favours ticagrelor but the direct evidence from ISAR-REACT 5 gave an odds ratio of 1.24 (0.90 to 1.70) which favours prasugrel. The committee therefore considered the pairwise data for the decision-making and took into the account the inconsistency identified. Health economic modelling also explored the implications of this inconsistency (treatment effects used can be seen in Table 18).

Following consideration of the pairwise meta-analyses the committee concluded that it was reasonable to assume that relative treatment effects were consistent and use the combined ACS population for the NMA given the same underlying disease process and an absence of a clear signal that relative treatment effects were different in different subgroups. For the purpose of the NMAs, all of the ACS populations were combined as heterogeneity was not identified in the pairwise meta-analyses. This suggests that the study populations did not differ in factors that interacted with the relative treatment effects.

Network diagram

For all the outcomes, the structure of the network meta-analyses was the same with direct evidence available for the comparisons: clopidogrel, prasugrel and ticagrelor (see Figure 1). The number of studies included in each comparison varied for each network meta-analysis can be seen in Table 6 . Full details can be found in the NMA write-up document.

Figure 1: Network structure



X = number of studies which would be included in each comparisons

Table 6: Number of studies included in each arm of the network meta-analysis

Outcomes	Ticagrelor versus Clopidogrel	Prasgurel versus Clopidogrel	Prasugrel versus Ticagrelor
All-cause mortality	5	4	5
New MI	6	2	3
Stroke	3	3	2
Major bleeding	4	2	3
Minor bleeding	5	1	4

Studies included in the network meta-analyses

Study and population	All-cause mortality	New myocardial infarction	Stroke	Major bleeding	Minor bleeding
Dehghani 2017[44] STEMI + revascularisation	✓	✓	-	✓	✓
Cannon 2007 (DISPERSE-2)[26] UA/STEMI	✓	✓	✓	✓	✓
Wallentin 2009 (PLATO)[284] ACS + with/without revascularisation	✓	✓	✓	✓	-

Roe 2012 (TRILOGY)[203] UA/NSTEMI + no revascularisation	✓	✓	✓	✓	-
Zeymer 2015 (ETAMI)[327] STEMI + revascularisation	✓	-	-	-	-
Montalescot 2009 (TRITON)[116] ACS + with revascularisation	✓	✓	✓	✓	✓
Alexopoulos 2012 [8] STEMI + revascularisation	✓	-	-	-	✓
Motovska 2016 (PRAGUE18)[119] ACS + with/without revascularisation	✓	✓	✓	✓	✓
Parodi 2013 (RAPID I)[185] STEMI + revascularisation	✓	✓	✓	✓	✓
Parodi 2014 (RAPID II)[184] STEMI + revascularisation	✓	-	-	✓	✓
Wang 2016b[289] STEMI + revascularisation	-	✓		-	-
Wang 2019[291] STEMI + revascularisation	✓	✓	-	✓	✓
Han 2019[56] STEMI + revascularisation	-	✓	-	-	✓
Bonello 2015[20] UA/NSTEMI + revascularisation	-	-	✓	✓	-
Jing 2016[65] STEMI + revascularisation	✓	-	-	-	✓
Dasbiswas 2013[36] ACS + revascularisation	✓	-		-	-
Laine 2014[84] UA/NSTEMI + revascularisation	✓		-	-	-

Summary of results

Table 7, Table 8, Table 9, Table 10, and Table 11 show the risk ratios calculated for the pairwise meta-analysis in this evidence review compared to the risk ratios calculated from the network meta-analysis. Additional summary statistics were calculated following the network meta-analysis, results can be seen in the NMA write-up document.

Table 7: Risk ratios for all-cause mortality at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model - median (95% credible intervals)
Ticagrelor	Clopidogrel	0.84 (0.70, 1.02)	0.85 (0.70, 1.02)
Prasugrel		0.83 (0.64, 1.06)	0.81 (0.64, 1.02)

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model - median (95% credible intervals)
Prasugrel	Ticagrelor	0.91 (0.50, 1.67)	0.96 (0.72, 1.26)

Table 8: Risk ratios for new myocardial infarction at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model (with pooled baseline estimate) - median (95% credible intervals)
Ticagrelor	Clopidogrel	0.69 (0.55, 0.86)	0.72 (0.56, 0.98)
Prasugrel		0.80 (0.65, 0.98)	0.83 (0.66, 1.00)
Prasugrel	Ticagrelor	1.31 (0.53, 3.23)	1.13 (0.89, 1.53)

Table 9: Risk ratios for stroke at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model (with pooled baseline estimate) - median (95% credible intervals)
Ticagrelor	Clopidogrel	1.32 (0.90, 1.93)	1.25 (0.86, 1.82)
Prasugrel		0.71 (0.40, 1.27)	0.81 (0.47, 1.39)
Prasugrel	Ticagrelor	2.24 (0.33, 15.06)	0.65 (0.34, 1.22)

Table 10: Risk ratios for major bleeding at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects - mean (95% confidence intervals)	NMA fixed effects (with pooled baseline estimate) – median (95% credible intervals)
Ticagrelor	Clopidogrel	1.00 (0.90, 1.11)	1.00 (0.90, 1.10)
Prasugrel		0.83 (0.48, 1.42)	0.98 (0.64, 1.46)
Prasugrel	Ticagrelor	1.37 (0.62, 3.02)	0.99 (0.64, 1.47)

Table 11: Risk ratios for minor bleeding at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model - median (95% credible intervals)
Ticagrelor	Clopidogrel	1.44 (0.99, 2.10)	1.25 (0.88, 1.77)
Prasugrel		0.61 (0.40, 0.93)	0.74 (0.52, 1.04)
Prasugrel	Ticagrelor	0.80 (0.48, 1.34)	0.59 (0.40, 0.87)

Conclusion

The committee reviewed the results for the five critical outcomes and noted that the evidence suggests that prasugrel and ticagrelor are both more clinically effective than clopidogrel for most of the outcomes. Prasugrel appeared more effective than ticagrelor in a majority of the outcome measures, but this difference was not clearcut and there was some uncertainty in the networks with overlapping credible intervals. For full details, see the NMA write-up document

1.6 Economic evidence

1.6.1 Included studies

Five health economic studies with relevant comparisons have been included in this review.[2,54,64,125,303] Note that two papers were identified for one study as one of these (Greenhalgh 2015[54]) is the evidence review group analysis for prasugrel TA317.[124] These are summarised in the health economic evidence profiles below (Table 12 to Table 15) and the health economic evidence tables in appendix H.

Note that as prasugrel is only indicated for people with ACS undergoing PCI the relevant comparators for an analysis vary by subpopulation. Ideally all clinical options should be included in an economic analysis to allow full incremental comparison; this would therefore be prasugrel, ticagrelor and clopidogrel in people undergoing PCI but only clopidogrel and ticagrelor with alternative management strategies.

1.6.2 Excluded studies

Eleven economic studies relating to this review question were identified but excluded due to methodological limitations or the availability of more applicable evidence.[37-39,51,55,57,102,168,189,267,295] These are listed in appendix I, with reasons for exclusion given.

See also the health economic study selection flow chart in appendix G.

1.6.3 Summary of studies included in the economic evidence review

Table 12: Health economic evidence profile: ticagrelor + aspirin versus prasugrel + aspirin versus clopidogrel + aspirin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Abdel-Qadir 2015[2] (Canada)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Markov cohort state transition model with baseline risks and treatment effects obtained from data collected in DISPERSE-2, PLATO and TRITON-TIMI 38 RCTs • Cost-utility analysis (QALYs) • Population: ACS (STEMI and UA/NSTEMI) patients who have undergone a PCI. • Comparators: ○ Intvn 1: Clopidogrel + aspirin ○ Intvn 2: Prasugrel + aspirin ○ Intvn 3: Ticagrelor + aspirin • Time horizon: lifetime	Intvn 2−1: £462[(c)] Intvn 3−2: £128[(c)]	Intvn 2−1: 0.02 QALYs Intvn 3−2: 0.07 QALYs	Intvn 3 vs 1: £6,556 per QALY gained Intvn 2: extendedly dominated	Probability most cost-effective option at £11,275/£16,912 threshold: Intervention 1: 17%/8% Intervention 2: 9%/8% Intervention 3: 74%/84% A wide range of sensitivity analyses around event rates, hazard ratios, utilities and costs were undertaken. This showed that varying the parameters did not impact the conclusions except for when the hazard ratio for death associated with ticagrelor relative to clopidogrel was greater than 0.89, which resulted in the ICER exceeding £28,187.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Wisloff 2016[303] (Norway)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Markov cohort state transition model with efficacy data of prasugrel and ticagrelor compared with clopidogrel based on the PLATO and TRITON-TIMI 38 RCTs • Cost-utility analysis was conducted as part of sensitivity analysis (QALYs); primary analysis used life years[(f)] • Population: ACS patients who have undergone a PCI • Comparators: ○ Intvn 1: Clopidogrel + aspirin ○ Intvn 2: Prasugrel + aspirin ○ Intvn 3:Ticagrelor + aspirin • Time horizon: lifetime	Intvn 2−1: £1,710[(g)] Intvn 3−2: £1,863[(g)]	Intvn 2−1: 0.36 life years Intvn 3−2: 0.38 life years Intvn 2−1: 0.28 QALYs Intvn 3−2: 0.30 QALYs	Intvn 3 vs 2: £6,210 per QALY gained Intvn 2 vs 1: £6,107 per QALY gained Intvn 3 is the most cost-effective option[(h)] Intvn 3 vs 2: £4,903 per life year gained Intvn 2 vs 1: £4,750 per life year gained	Probability most cost-effective option for QALY results: NR Probability most cost effective option (£31,428 threshold per life year gained): Intervention 3: 76% Intervention 2: 27% A range of scenario analyses were conducted for the results in relation to cost per life year gained and showed that ticagrelor remained cost-effective in all scenarios.

Abbreviations: ACS = acute coronary syndromes; ICER= incremental cost-effectiveness ratio; PCI = percutaneous coronary intervention; QALY= quality-adjusted life years; RCT= randomised controlled trial

(a) 2012 Canadian healthcare perspective may not reflect the current UK context, the cost of clopidogrel used in the model is higher than the cost in the UK, discount rate used not in line with NICE reference case methods and unclear if methods used to derive utilities are consistent with NICE reference case methods.

(b) Health states incorporated in the model were different from other models in this area (it does not include stroke as a health state which is a limitation), baseline risks were obtained by calculating the weighted mean of the event rates in the clopidogrel arm of the 3 international trials and the average age used was lower than the UK average. It is unclear where information on resource use was obtained and the analysis does not reflect full body of available evidence for this area as identified in clinical review (based on 3 trials)

(c) 2012 Canadian dollars converted to UK pounds.[175] Cost components included: drug costs, hospitalisation, major bleed, consultations with an emergency physician, a cardiologist and an interventional cardiologist, angiography and percutaneous coronary intervention, transthoracic echocardiogram, follow-up appointments

(d) 2014 Norwegian healthcare perspective may not reflect the current UK context, the cost of clopidogrel used in the model is higher than the cost in the UK, EQ-5D used but unclear if fully in line with NICE reference case methods as tariff not reported and population collected in not stated.

(e) Health states incorporated in the model were different from other models in this area (it does not include stroke as a health state which is a limitation), did not give details of how baseline risks were derived, average age used in the model is lower than UK average, it is unclear where resource use was obtained, only conducted sensitivity analyses on results related to life years and not QALYs. Analysis does not reflect full body of available evidence for this area as identified in clinical review (based on 2 trials)

(f) QALY results are presented as this is the preferred outcome as per the NICE reference case; life year results also presented as uncertainty is only reported for this analysis.

(g) 2014 Norwegian kroner converted to UK pounds [175] Cost components included: drug costs, costs of treatment (MI, revascularisation and bleeding), GP visits and laboratory test costs.

(h) When comparing multiple comparators, a fully incremental approach is adopted that compares the treatments sequentially in rank order of effectiveness (or cost). Incremental cost-effectiveness ratios are estimated by dividing the incremental cost by the incremental effect for each consecutively more effective comparator.

Table 13: Health economic evidence profile: ticagrelor + aspirin versus clopidogrel + aspirin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE TA236 2011 *Manufacturer submission* [125] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Decision tree based on within-trial analysis of the PLATO RCT to model first year, followed by Markov model to extrapolate • Cost utility analysis (QALYs) • Comparators: ○ Clopidogrel + aspirin ○ Ticagrelor + aspirin • Population: adults with ACS (STEMI, NSTEMI and UA), including those managed medically	*All ACS:* £405[(c)] *STEMI:* £339[(c)] *NSTEMI:* £512[(c)] *UA:* £488[(c)]	*All ACS:* 0.106 QALYs *STEMI:* 0.120 QALYs *NSTEMI:* 0.098 QALYs *UA:* 0.091 QALYs	*All ACS:* £3,805 per QALY gained *STEMI:* £2,825 per QALY gained *NSTEMI:* £5,230 per QALY gained *UA:* £5,374 per QALY gained	*Probability ticagrelor cost effective (£20K/£30K threshold):* *All ACS:* 99.9%/NR *STEMI:* NR/NR *NSTEMI:* NR/NR *UA:* NR/NR A wide range of sensitivity analyses around event rates, hazard ratios, utilities and costs were undertaken. This showed that varying the parameters did not impact the

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			or those with PCI or CABG • Time horizon: lifetime				conclusions apart from the cost of the 'no further event' health state, where ticagrelor became dominant if the lowest value for the cost of ticagrelor was used. Where the lowest value was used for clopidogrel, ticagrelor was borderline cost-effective. See Table 16 for additional scenario analyses
Janzon 2015[64] (UK)	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Decision tree based on within-trial analysis of the PLATO RCT to model first year, followed by Markov model to extrapolate • Cost utility analysis (QALYs) • Comparators: ○ Clopidogrel + aspirin ○ Ticagrelor + aspirin • Population: adults with ACS intended for non-invasive therapy but could undergo	£468[(g)]	0.16 QALYs	£2,925 per QALY gained	*Probability ticagrelor cost effective (£20K/£30K threshold):* 99.9%/99.9% Alternative scenarios were explored by altering the value of input parameters not associated with sampling uncertainty (therefore not varied in the probabilistic sensitivity analysis). These scenarios did not change conclusions about cost effectiveness.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			revascularisation if necessary[f] • Time horizon: lifetime				

Abbreviations: ACS = Acute coronary syndrome; CABG = coronary artery bypass graft; NR = not reported; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention; QALY = quality-adjusted life years; RCT = randomised controlled trial; STEMI = ST-elevation myocardial infarction; UA = unstable angina

(a) International resource use from 2006-2008 and 2008/09 UK unit costs may not reflect current UK practice. UK practice is to give a clopidogrel loading dose of 600mg and the study allowed a clopidogrel loading dose of 300-600mg with only one fifth of patients received 600mg. Does not do a three way comparison including prasugrel for those who are eligible for it.

(b) Mean age of patients in the PLATO trial was lower than UK average and proportion of older patients different to UK setting but an age-adjusted event rate was used in the clopidogrel arm to attempt to address this. Analysis does not reflect full body of available evidence for this area as identified in clinical review; main analysis based on a single study (PLATO). Uncertainty in estimates of effectiveness due to participants being able to leave the trial early and not followed up for 12 months - which affects the long-term patient outcomes in the Markov model. The health economic sub-study was used to derive data on resource use and utilities; however there was no information on how this sub-study was recruited for. Study funded by AstraZeneca.

(c) Cost components included: drug costs (ticagrelor, clopidogrel, prasugrel and aspirin), hospitalisation, investigations, blood products and reoperations due to bleeding and drugs, event costs (stroke and myocardial infarction).

(d) International resource use from 2006-2008 and 2010 UK unit costs may not reflect current UK practice. Only looks at patients intended for non-invasive management. Start age used in the cohort is younger than the average age of UK ACS patients.

(e) Does not state if bleeding was incorporated in the model, analysis does not reflect full body of available evidence for this area as identified in clinical review; analysis based on a single study (PLATO). Study was funded by AstraZeneca.

(f) Although patients were intended for non-invasive management approximately half of the patients had coronary angiography, a third had PCI, and one tenth had CABG during the course of the study. 9% of patients had STEMI, 56% had NSTEMI and 35% had unstable angina/other.

(g) Cost components included: drug costs (ticagrelor, clopidogrel and aspirin), bed days due to hospitalisation, investigations, blood product and reoperations due to bleeding and event costs (stroke and MI).

Table 14: Health economic evidence profile: ticagrelor + aspirin versus prasugrel + aspirin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NICE TA236 2011 (UK) *Manufacturer submission*[12 5]	Partially applicable[a]	Potentially serious limitations[b]	• Decision tree for the first year, followed by Markov model, based on an indirect comparison of ticagrelor and prasugrel from PLATO	£277[c]	0.065 QALYs	£3,482 per QALY gained	*Probability ticagrelor cost effective (£20K/£30K threshold):* 91.6%/NR Deterministic results using a different time horizon showed that ticagrelor

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			and TRITON-TIMI 38 RCTs[18] • Cost utility analysis (QALYs) • Comparators: ○ Prasugrel + aspirin ○ Ticagrelor + aspirin • Population: ACS patients managed invasively (angiography followed by PCI/CABG if indicated) • Time horizon: lifetime				remained cost-effective at 20, 10 and 5 years as demonstrated in Table 16.

Abbreviations: ACS = Acute coronary syndrome; CABG = coronary artery bypass graft; NR = not reported; PCI = percutaneous coronary intervention; QALY = quality-adjusted life years; RCT = randomised controlled trial

(a) International resource use from PLATO RCT which recruited 2006-2008 and 2008/09 UK unit costs may not reflect current UK practice. Does not include clopidogrel in the analysis.

(b) Baseline event rates were taken from the PLATO international trial, which may not reflect UK practice, however the analysis used an age-adjusted event rate to address this. Relative treatment effects for prasugrel compared to ticagrelor were estimated from an indirect comparison using studies that compared each drug to clopidogrel; while using an indirect comparison is not necessarily inappropriate the manufacturer highlighted issues with the indirect comparison and the technology appraisal committee did not think the analysis was appropriate due to differences in the target populations of the two trials, differences in the usage of clopidogrel (dosing and timing) and differences in the assessment of MI. Health state costs were calculated based on resource use collected in ticagrelor arm of the PLATO trial; in the absence of a head-to-trial collecting such data, it was assumed that these costs would be the same with prasugrel. Study was funded by AstraZeneca.

(c) Cost components included: drug costs (ticagrelor, prasugrel and aspirin), hospitalisation, investigations, blood products and reoperations due to bleeding and drugs, event costs (stroke and MI).

Table 15: Health economic evidence profile: prasugrel + aspirin versus clopidogrel + aspirin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Greenhalgh 2015[54] (UK) *ERG analysis for NICE TA317*[124]	Partially applicable[(a)]	Potentially serious limitations[(b)]	• Markov model structure with two phases; the first phase models the within-trial period of the TRITON-TIMI 38 RCT and the second phase extrapolates beyond one year and is based on the CAPRIE RCT • Cost-utility analysis (QALYs) • Comparators: ○ Clopidogrel + aspirin ○ Prasugrel + aspirin • Population: ACS patients managed with PCI • Time horizon: lifetime	*STEMI patients with diabetes:* £447 *STEMI patients without diabetes:* £555 *UA/NSTEMI patients with diabetes:* –£77 *UA/NSTEMI patients without diabetes:* £248	*STEMI patients with diabetes:* 0.28 QALYs *STEMI patients without diabetes:* 0.08 QALYs *UA/NSTEMI patients with diabetes:* 0.18 QALYs *UA/NSTEMI patients without diabetes:* 0.05 QALYs	*STEMI patients with diabetes:* £1,732 per QALY gained *STEMI patients without diabetes:* £7,073 per QALY gained *UA/NSTEMI patients with diabetes:* Prasugrel dominant *UA/NSTEMI patients without diabetes:* £4,154 per QALY gained	*Probability prasugrel cost effective (£20K/£30K threshold):* *STEMI patients with diabetes:* NR/NR *STEMI patients without diabetes:* NR/NR *UA/NSTEMI patients with diabetes:* NR/NR *UA/NSTEMI patients without diabetes:* NR/NR Univariate sensitivity analyses were performed on all model variables subject to uncertainty, and prasugrel remained cost-effective. Different time horizons were explored and are presented in Table 17.

Abbreviations: ACS = acute coronary syndromes; ERG = evidence review group; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; QALY= quality-adjusted life years; RCT= randomised controlled trial; STEMI = ST segment elevation myocardial infarction; UA = unstable angina

(a) International resource use from 2004-2007 and 2012 UK unit costs may not reflect current UK practice. The trial used a clopidogrel loading dose of 300mg instead of 600mg which does not reflect UK practice and analysis does not include ticagrelor.

(b) Mean age of patients in the TRITON-TIMI 38 trial was different to UK average but this was accounted for by adjusting the initial health state utilities of each subgroup. Did not use new cost data for the relevant year; instead unit costs from the previous TA report were inflated to 2012 prices. Analysis does not reflect full body of available evidence identified in clinical review, main analysis based on a single study (TRITON-TIMI 38).

(c) Cost components included: drug costs, repeat hospitalisations, health care costs associated events (fatal MI, non-fatal MI, fatal stroke, non-fatal non –disabling stroke, non-fatal disabling stroke, non-vascular death, and other vascular death).

Additional results from the ticagrelor manufacturer submission are summarised in Table 16 below.

Table 16: Incremental cost-effectiveness ratios with different time horizons in NICE TA236

Time horizon	Ticagrelor versus clopidogrel				Ticagrelor versus prasugrel
	All ACS	STEMI	NSTEMI	UA	
Lifetime	£3,696	£2,825	£5,230	£5,374	£3,482
20 years	£3,705	£2,847	£5,233	£5,410	£3,598
10 years	£4,182	£3,334	£5,727	£6,484	£4,562
5 years	£6,075	£4,946	£8,162	£10,172	£7,047
1 year	£36,177	£31,933	£45,810	£78,288	NR

Abbreviations: NR = not reported

Additional results from the prasugrel ERG report are summarised in Table 17 below.

Table 17: Incremental cost-effectiveness ratios with different time horizons in Greenhalgh 2015

Time horizon	Prasugrel versus clopidogrel			
	STEMI with diabetes	STEMI without diabetes	UA/NSTEMI with diabetes	UA/NSTEMI without diabetes
Lifetime	£1,640	£6,626	Dominant	£4,667
20 years	£1,537	£7,670	Dominant	£5,688
10 years	£2,139	£13,370	Dominant	£14,276
5 years	£4,603	£29,607	£2,846	£52,288
1 year	£31,915	£224,302	£76,856	£1,101,662

1.6.4 Health economic modelling

The committee agreed that which DAPT option to use in people with ACS undergoing PCI was the highest priority for new economic analysis. This was due to there being variation in current practice and substantial differences in the cost of the interventions. Therefore, a recommendation for a particular agent would result in a significant change in clinical practice that could have a substantial resource impact to the NHS in England.

Model methods

A technical report for this analysis including full details of all methods and model inputs is available in a separate document 'Health Economic Analysis DAPT'. A summary is provided below.

A cost-utility analysis was undertaken to compare asprin plus one of clopidogrel, prasugrel or ticagrelor for people with UA/NSTEMI or STEMI undergoing PCI from a current UK NHS and personal social services perspective. A two-part model was constructed which included a decision tree to model events in the first year followed by a Markov model for long term extrapolation in order to calculate lifetime costs and QALYs. Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance. An incremental analysis was undertaken.

The comparators selected for the model were:

- Clopidogrel 75mg once daily + aspirin 75-150mg once daily (300-600mg clopidogrel loading dose) for 12 months
- Prasugrel 5-10mg once daily + aspirin 75-150mg once daily (60mg prasugrel loading dose) for 12 months
- Ticagrelor 90mg twice daily + aspirin 75-150mg once daily (180mg ticagrelor loading dose) for 12 months

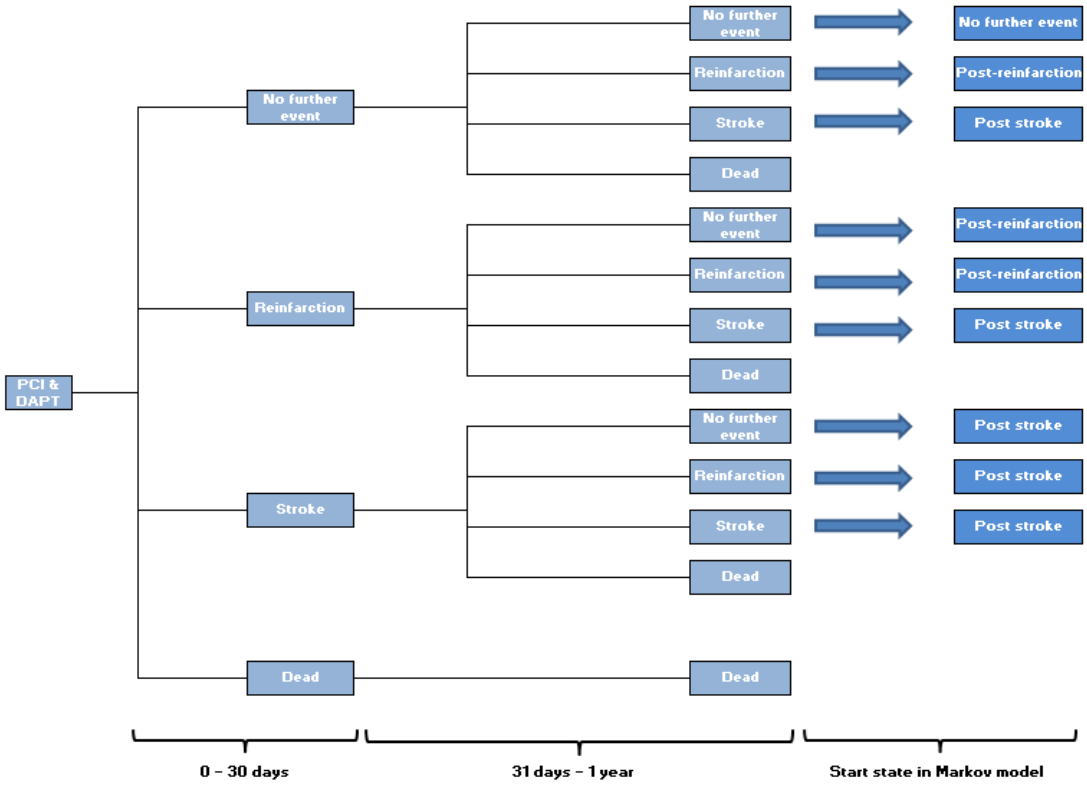
The population considered in the analysis was adults with UA/NSTEMI or STEMI undergoing PCI. STEMI and UA/NSTEMI were modelled separately as baseline risks were considered likely to be different, although relative treatment effects were assumed to be the same following consideration of the clinical evidence review. The economic analysis did not consider people with UA/NSTEMI that are medically managed. This is because prasugrel is not indicated in this population and two published UK economic analyses indicated that ticagrelor is cost-effective compared to clopidogrel in this population and additional economic analyses was not considered necessary.

Following review of the clinical evidence, it was agreed that the following outcomes should be captured in the 1 year model as they potentially vary between DAPT options:

- All-cause mortality
- Reinfarction
- Stroke
- Major bleed
- Minor bleed

The initial decision tree was broken down into two time periods, 0 to 30 days and 31 days to 1 year, in order to make best use of the available clinical data. The decision tree comprised four potential health states including no further event, reinfarction, stroke and death. Major and minor bleeding were incorporated as adverse events as the effects were considered to have a short-term impact. Figure 2 shows the structure of the decision tree.

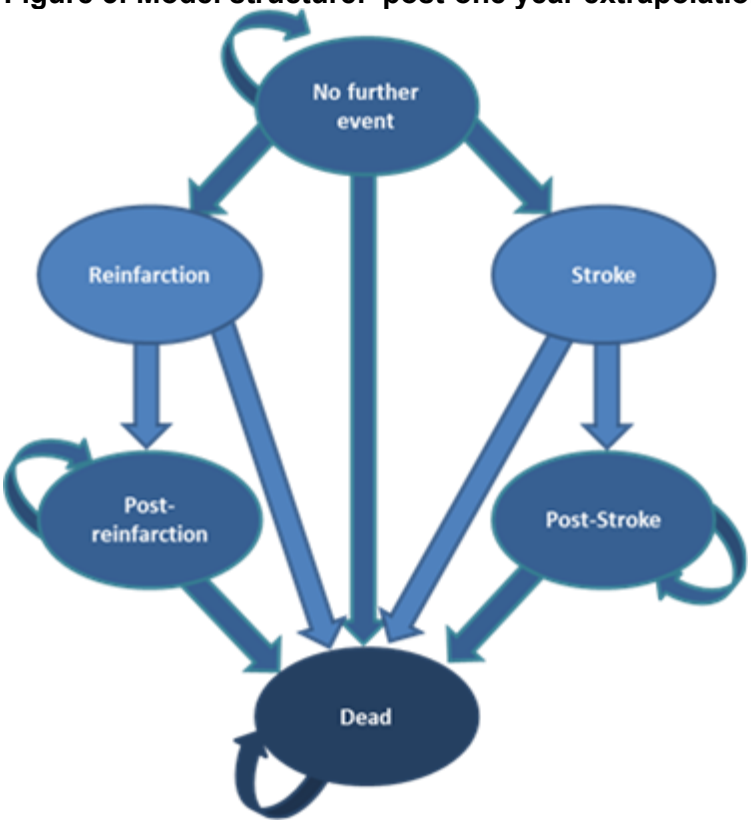
Figure 2: Model structure: one year treatment period decision tree



Notes: Probabilities of events are dependent on DAPT being received. People who are alive are also at risk of a short-term major or minor bleeding adverse event.

People alive at the end of the 1 year decision tree entered the post-one year Markov model to extrapolate 1 year outcomes to a lifetime perspective. Figure 3 shows the structure of the Markov model. The Markov model consisted of six health states: no further event, reinfarction, post-reinfarction, stroke, post-stroke and dead. Those that experienced no further event at the end of the decision tree entered the 'no further event' health state in the Markov model. Those that had reinfarction (either once or twice) at the end of the decision tree entered the 'post-reinfarction' health state. Those that had a stroke at the end of the decision tree or had both a stroke and reinfarction entered the 'post-stroke' health state. Those in the no further event health state could only go on to have one event (reinfarction or stroke). Once someone entered the post-reinfarction or post-stroke health state, they could not experience a second event. Transition probabilities in the Markov model were the same irrespective of the DAPT received in year 1, however as the number of people entering the Markov in each state will vary (that is the number of people who have died, had an MI and had a stroke by one year), costs and QALYs will continue to vary between DAPT groups after one year.

Figure 3: Model structure: post-one year extrapolation Markov model



Note: 1 year cycles; model was run for 40 years at which point most people will be in the dead state; the state people enter model depends on events experienced in year 1 decision tree.

Model inputs are described in full in the separate technical report. In summary, baseline risks were sourced from published analyses using national audit data where possible to reflect real world risks in people with ACS undergoing PCI in England. Relative treatment effects were based on the systematic review and meta analyses of RCTs undertaken for this guideline update. UK costs were used. Health-related quality of life weights were based on the published literature.

The unit costs of aspirin, clopidogrel, prasugrel and ticagrelor that are used in the model shown in Table 18. DAPT costs varied by comparator in the first year.

Table 18: Model inputs: DAPT costs

Drug	Loading dose	Loading dose cost	Daily maintenance dose	Cost per day	Cost per year
Aspirin	n/a	n/a	75mg	£0.07	£23.99
Clopidogrel	300mg	£0.24	75mg	£0.06	£21.64
	600mg	£0.47	75mg	£0.06	£21.64
Prasugrel	60mg	£1.36	5mg	£0.51	£187.71
			10mg	£0.23	£82.65
Ticagrelor	180mg	£1.95	180mg	£1.95	£711.75

Source: doses from British National Formulary[67], accessed 1st July 2020; unit costs from NHS Drug Tariff July 2020[166]

The model was populated with baseline risks for those receiving clopidogrel and asprin (e.g. the probability of death at 30 days). When running the model for those receiving ticagrelor and prasugrel a relative treatment effect obtained from the clinical review and evidence

syntheses (compared to clopidogrel) was applied to this in order to estimate the difference in number of events with these alternative treatments. Costs and clinical events therefore vary by comparator.

The relative treatment effects applied in the model are summarised in Table 19. For the 0 – 30 day period odds ratios were obtained from the network meta-analysis at 30 days which combined RCT evidence for ticagrelor versus clopidogrel, prasugrel versus clopidogrel and ticagrelor versus prasugrel into a single set of consistent relative treatment effects. Network meta-analysis combining all available data was not reliable for 1 year outcomes due to inconsistency in the network and so three different data scenarios were analysed using different set of data. This resulted in three data scenarios. The relative treatment effects for each scenario are shown in the table. For each scenario the black text indicates the direct data used and the grey text shows the implied relative treatment effects for the remaining comparison. Note that ISAR-REACT 5 (that compared prasugrel and ticagrelor at 1 year) did not report minor bleeding and so relative treatment effects in scenarios 2 and 3 remain the same as in scenario 1.

Table 19: Model inputs: relative treatment effects

	30 days (all scenarios_	1 year		
		Scenario 1	Scenario 2	Scenario 3
Data used	Network meta-analysis OR (95% CI)	Ticagrelor vs clopidogrel (meta-analysis) Prasugrel vs clopidogrel (meta-analysis) OR (95% CI)	Prasugrel vs clopidogrel (meta-analysis) Ticagrelor versus prasugrel (ISAR REACT 5) OR (95% CI)	Ticagrelor vs clopidogrel (meta-analysis) Ticagrelor versus prasugrel (ISAR REACT 5) OR (95% CI)
Ticagrelor vs clopidogrel				
All-cause mortality	0.85 (0.70 to 1.02)	0.77 (0.68 to 0.88)	1.24 (0.86 to 1.79)	0.77 (0.68 to 0.88)
Reinfarction	0.68 (0.55 to 0.84)	0.82 (0.73 to 0.92)	1.22 (0.87 to 1.73)	0.82 (0.73 to 0.92)
Stroke	1.28 (0.86 to 1.83)	1.13 (0.89 to 1.44)	1.08 (0.54 to 2.17)	1.13 (0.89 to 1.44)
Major bleed	1.00 (0.89 to 1.11)	1.04 (0.95 to 1.14)	1.52 (1.04 to 2.22)	1.04 (0.95 to 1.14)
Minor bleed	1.28 (0.88 to 1.81)	1.37 (1.19 to 1.57)	1.37 (1.19 to 1.57)[(a)]	1.37 (1.19 to 1.57)
Prasugrel vs clopidogrel				
All-cause mortality	0.81 (0.63 to 1.02)	1.00 (0.83 to 1.21)	1.00 (0.83 to 1.21)	0.62 (0.44 to 0.87)
Reinfarction	0.80 (0.65 to 0.98)	0.75 (0.66 to 0.84)	0.75 (0.66 to 0.84)	0.50 (0.36 to 0.71)
Stroke	0.84 (0.46 to 1.39)	0.93 (0.67 to 1.30)	0.93 (0.67 to 1.30)	0.97 (0.50 to 1.88)
Major bleed	0.99 (0.61 to 1.52)	1.43 (1.14 to 1.79)	1.43 (1.14 to 1.79)	0.98 (0.71 to 1.35)
Minor bleed	0.74 (0.51 to 1.04)	2.07 (0.88 to 4.87) [(a)]	2.07 (0.88 to 4.87) [(a)]	2.07 (0.88 to 4.87)[(a)]
Ticagrelor vs prasugrel				
All-cause mortality	1.04 (0.79 to 1.39)	0.77 (0.61 to 0.97)	1.24 (0.90 to 1.70)	1.24 (0.90 to 1.70)
Reinfarction	0.84 (0.64 to 1.14)	1.08 (0.92 to 1.27)	1.63 (1.17 to 2.26)	1.63 (1.17 to 2.26)
Stroke	1.47 (0.82 to 2.98)	1.22 (0.80 to 1.84)	1.16 (0.62 to 2.14)	1.16 (0.62 to 2.14)
Major bleed	1.00 (0.65 to 1.64)	0.73 (0.57 to 0.93)	1.06 (0.78 to 1.44)	1.06 (0.78 to 1.44)
Minor bleed	1.69 (1.16 to 2.59)	0.66 (0.28 to 1.57)[(b)]	0.66 (0.28 to 1.57) [(b)]	0.66 (0.28 to 1.57) [(b)]

Abbreviations: 95% CI = 95% confidence interval; OR = odds ratio.

Note: For 1 year data, black text indicates the direct data used in that particular scenario and grey text shows the implied relative treatment effects for the remaining comparison. All text is black in the 0 to 30 days column as an NMA was used to combine all data into a single set of consistent treatment effects.

(a) ISAR-REACT 5 did not report minor bleeding therefore treatment effects remained the same as scenario 1.

(b) These estimates are the implied treatment effects for minor bleeding using the data for ticagrelor versus clopidogrel and prasugrel versus clopidogrel

Source: Systematic review and meta analyses of RCTs undertaken for the guideline update, see 'Clinical evidence' section for details.

The model was built probabilistically to account for the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 5000 times for the base-case analysis and each sensitivity analysis – and results were summarised in terms of mean costs and QALYs, and the percentage of time each comparator was the most cost-effective strategy at a threshold of £20,000/£30,000 per QALY gained.

In addition, various one way and scenario sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

Results

Base case analysis results are presented in Table 20. Results are presented for the three scenarios that utilise different data to inform the relative treatment effects at 1 year in the model (all scenarios also use the 30-day NMA to inform the relative treatment effects 0 to 30 days in the model):

1. Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)
2. Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)
3. Ticagrelor vs clopidogrel (meta-analysis); Ticagrelor versus prasugrel (ISAR-REACT 5)

In the base case analysis, the DAPT option that was most cost effective varied depending on the clinical data used to inform the 1-year relative treatment effects. Ticagrelor was the most cost effective DAPT option for both STEMI and UA/NSTEMI when 1-year relative treatment effects in the model were based on studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel (data scenario 1). Within this scenario, there was low uncertainty in this conclusion with ticagrelor being the most cost effective option 93%/86% of the time for STEMI and UA/NSTEMI respectively. However, prasugrel was the most cost effective option for both STEMI and UA/NSTEMI when 1 year relative treatment effect data from ISAR-REACT 5 was incorporated in the model (data scenarios 2 and 3). There was low uncertainty in this conclusion within scenario 3 with prasugrel being the most cost effective option 96%/98% of the time for STEMI and UA/NSTEMI respectively. There was moderate uncertainty within scenario 2 with prasugrel being the most cost effective option 58%/60% of the time, but clopidogrel being the most cost effective option 37%/38% of the time for STEMI and UA/NSTMEI respectively.

Ticagrelor had the highest costs in all scenarios and ACS subgroups but only had the highest QALYs in scenario 1. In scenarios 2 and 3, prasugrel had lower costs than ticagrelor and also higher QALYs; QALYs are greater with prasugrel in these scenarios as when ISAR-REACT 5 was incorporated ticagrelor had a greater number of all clinical events (except minor bleeding) than prasugrel in the first year. Clopidogrel had the lowest costs in all scenarios and had the lowest QALYs in scenarios 1 and 3 for STEMI and UA/NSTEMI; in scenario 2 ticagrelor had the lowest QALYs. The reason ticagrelor had the lowest QALYs in scenario 2 was because 1 year events with ticagrelor were greater than with clopidogrel in

this scenario. This scenario inferred the relative treatment effects of ticagrelor versus clopidogrel from the prasugrel versus clopidogrel meta-analysis and the ticagrelor versus prasugrel data. All details of relative treatment effects can be seen in the methods section but for example, at 1 year ticagrelor had greater mortality than prasugrel in the ISAR-REACT 5 trial and prasugrel had the same mortality as clopidogrel in the meta-analysis, therefore using this data ticagrelor had great mortality than clopidogrel.

In all scenarios the main driver of the higher costs with ticagrelor and lower costs with clopidogrel was the intervention costs, as the intervention costs associated with ticagrelor was around £600 more than clopidogrel for both STEMI and UA/NSTEMI. As prasugrel had the second highest intervention costs, this resulted in prasugrel having the second highest lifetime costs.

Table 20: Base case analysis results (probabilistic analysis) – cost effectiveness results (mean per person)

Intervention	Mean lifetime costs undisc	Mean lifetime costs disc	Mean life years	Mean lifetime QALYs Undisc	Mean lifetime QALYs disc	Incr. cost	Incr. QALYs	ICER	NMB (£20k)*	Rank at £20k*	% CE at £20k*	% Rank 2nd (£20k)*	% Rank 3rd (£20k)*	% CE at £30k**
Scenario 1 – Ticagrelor vs clopidogrel (meta-analysis); prasugrel vs clopidogrel (meta-analysis)														
STEMI														
Clopidogrel	£23,068	£17,336	13.05	8.29	6.42				£111,149	3	0%	40%	60%	0%
Prasugrel	£23,137	£17,385	13.08	8.31	6.44	£49	0.01	£3,507	£111,381	2	7%	54%	40%	4%
Ticagrelor	£24,299	£18,387	13.36	8.48	6.57	£1,002	0.13	£7,455	£113,067	1	93%	7%	0%	96%
UA/NSTEMI														
Clopidogrel	£19,327	£14,854	12.95	8.21	6.44				£113,954	3	0%	40%	60%	0%
Prasugrel	£19,370	£14,892	12.97	8.22	6.45	£38	0.01	£4,510	£114,085	2	14%	46%	39%	7%
Ticagrelor	£20,216	£15,665	13.12	8.32	6.52	£774	0.07	£10,424	£114,795	1	86%	14%	0%	93%
Scenario 2 – Prasugrel vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	£23,115	£17,368	13.05	8.29	6.42				£111,106	2	37%	58%	5%	36%
Prasugrel	£23,188	£17,420	13.08	8.31	6.44	£52	0.01	£3,615	£111,343	1	58%	36%	6%	58%
Ticagrelor	£23,303	£17,702	12.75	8.10	6.28	£282	-0.16	Dominated	£107,887	3	5%	6%	90%	6%
UA/NSTEMI														
Clopidogrel	£19,359	£14,874	12.95	8.21	6.44				£113,936	2	38%	60%	2%	37%
Prasugrel	£19,403	£14,914	12.97	8.22	6.45	£39	0.01	£4,525	£114,071	1	60%	37%	4%	59%
Ticagrelor	£19,810	£15,386	12.78	8.10	6.36	£472	-0.09	Dominated	£111,732	3	2%	4%	94%	4%
Scenario 3 – Ticagrelor vs clopidogrel (meta-analysis); ticagrelor versus prasugrel (ISAR-REACT 5)														
STEMI														
Clopidogrel	£23,101	£17,362	13.05	8.29	6.42				£111,091	3	0%	0%	100%	0%

Prasugrel	£23,996	£17,983	13.57	8.62	6.67	£620	0.25	£2,469	£115,495	1	96%	4%	0%	95%
Ticagrelor	£24,331	£18,413	13.36	8.48	6.57	£430	-0.10	Dominated	£112,994	2	4%	96%	0%	5%
UA/NSTEMI														
Clopidogrel	£19,374	£14,890	12.96	8.21	6.44				£113,893	3	0%	1%	99%	0%
Prasugrel	£19,774	£15,175	13.25	8.40	6.58	£286	0.14	£1,979	£116,493	1	98%	2%	0%	97%
Ticagrelor	£20,262	£15,701	13.12	8.32	6.52	£526	-0.06	Dominated	£114,727	2	2%	98%	1%	3%

Abbreviations: CE = cost effective; disc. = discounted; Incr. = incremental; NMB = net monetary benefit; QALY = quality-adjusted life years; undisc = undiscounted; £20K = threshold of £20,000 per QALY gained; £30K = a threshold of £30,000 per QALY gained.

In addition to probabilistic sensitivity analysis, a range of one-way and scenario sensitivity analysis were undertaken including varying the baseline risk of stroke, inclusion of stroke treatment effects, inclusion of dyspnoea as a side effect, varying bleeding and stroke costs, varying dosing assumptions, incorporation of post-ACS rivaroxaban use, varying event-related mortality in the extrapolation model, varying the baseline risk of stroke and reinfarction to account for overestimation of people alive with an event and varying intervention costing assumptions. The conclusions did not change in the majority of sensitivity analyses, the exception being the exploratory sensitivity analysis in which rivaroxaban was assumed to be used in all people receiving clopidogrel, in which case clopidogrel (incorporating rivaroxaban) became the most cost effective option in scenario 1 and 2; prasugrel remained the most cost effective option in scenario 3. When rivaroxaban usage was assumed to be 1.8% (as estimated current practice is among people receiving clopidogrel) conclusions about which DAPT option was the most cost effective remained the same as in the base case analyses in all scenarios.

All results and a full discussion of limitations and interpretation of the analysis are included in the full technical report for this analysis available in a separate document 'Health Economic Analysis DAPT'. The committee's discussion and interpretation is summarised in section 1.8 of this report.

1.7 Evidence statements

1.7.1 Clinical evidence statements

Ticagrelor versus clopidogrel

ACS with/without revascularisation

- There was a clinically important benefit of ticagrelor compared to clopidogrel for all-cause mortality at 30 days (1391 participants in 5 studies, very low quality evidence) and in all-cause mortality at 1 year (20443 participants in 6 studies, low quality evidence) for ACS with/without revascularisation.
- There was a clinically important harm in cardiac mortality at 30 days (1143 participants in 4 studies, very low quality evidence) when ticagrelor + aspirin was compared to clopidogrel. There was however a clinically important benefit of ticagrelor compared to clopidogrel for cardiac mortality at 1 year (20711 participants in 6 studies, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference of ticagrelor compared to clopidogrel for re-infarction at 30 days (1397 participants in 5 studies, low quality evidence). There was however a clinically important benefit of ticagrelor compared to clopidogrel for re-infarction at 1 year (21129 participants in 8 studies, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for major bleeding at 30 days (1411 participants in 5 studies, very low quality evidence) and major bleeding at 1 year (20206 participants in 6 studies, moderate quality evidence) for ACS with/without revascularisation.
- There was a clinically important increase in minor bleeding at 30 days (1511 participants in 6 studies, low quality evidence) when ticagrelor was compared to clopidogrel. There was however no clinically important difference between ticagrelor and clopidogrel for minor bleeding at 1 year (20384 participants in 6 studies, very low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stroke at 30 days (979 participants in 3 studies, very low quality evidence) and stroke at 1 year

(20711 participants in 6 studies, moderate quality evidence) for ACS with/without revascularisation.

- There was a clinically important benefit of ticagrelor compared to clopidogrel for need for revascularisation at 1 year (1260 participants in 4 studies, moderate quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stent thrombosis (type not specified) at 1 year (1086 participants in 3 studies, moderate quality evidence) and stent thrombosis (definite and probable) at 1 year (11289 participants in 1 study, low quality evidence) for ACS with/without revascularisation.
- There was a clinically important increase in breathing adverse effects at 1 year (19222 participants in 2 studies, moderate quality evidence) when ticagrelor was compared to clopidogrel for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for bradycardiac adverse effects at 30 days (2309 participants in 3 studies, very low quality evidence) and bradycardiac adverse effects at 1 year (13632 participants in 3 studies, moderate quality evidence) for ACS with/without revascularisation.
- There was a clinically important increase in other adverse effects at 30 days (324 participants in 2 studies, very low quality evidence) and when ticagrelor was compared to clopidogrel. There was however no clinically difference between ticagrelor and clopidogrel for other adverse effects at 1 year (19342 participants in 3 studies, moderate quality evidence) for ACS with/without revascularisation.

UA/NSTEMI - with/without revascularisation

With revascularisation

- There was a clinically important benefit of ticagrelor compared to clopidogrel for all-cause mortality at 30 days (6218 participants in 1 study, low quality evidence) and in all-cause mortality at 1 year (5648 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for cardiac mortality at 30 days (6218 participants in 1 study, low quality evidence) and in cardiac mortality at 1 year (5648 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for re-infarction at 30 days (5934 participants in 1 study, very low quality evidence) and re-infarction at 1 year (5438 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for major bleeding at 30 days (4958 participants in 1 study, very low quality evidence) and major bleeding at 1 year (4983 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was a clinically important increase of bleeding (type not specified) at 1 year when ticagrelor was compared to clopidogrel (244 participants in 1 study, low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stroke at 30 days (6188 participants in 1 study, very low quality evidence) and stroke at 1 year (5632 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stent thrombosis (type not specified) at 1 year (442 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.

Without revascularisation

- There was a clinically important benefit of ticagrelor compared to clopidogrel for all-cause mortality at 30 days (4514 participants in 1 study, low quality evidence) and in all-cause mortality at 1 year (5217 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for cardiac mortality at 30 days (4514 participants in 1 study, low quality evidence) and in cardiac mortality at 1 year (5217 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for re-infarction at 30 days (4479 participants in 1 study, very low quality evidence) and re-infarction at 1 year (5201 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for major bleeding at 30 days (3964 participants in 1 study, very low quality evidence) and major bleeding at 1 year (4931 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stroke at 30 days (4502 participants in 1 study, very low quality evidence) and stroke at 1 year (5209 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.

STEMI with revascularisation

- There was a clinically important benefit of ticagrelor compared to clopidogrel for all-cause mortality at 30 days (630 participants in 3 studies, low quality evidence) and in all-cause mortality at 1 year (8242 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for cardiac mortality at 30 days (482 participants in 3 studies, very low quality evidence) and in cardiac mortality at 1 year (8630 participants in 4 studies, low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for re-infarction at 30 days (736 participants in 4 studies, low quality evidence) and in re-infarction at 1 year (8928 participants in 5 studies, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and to clopidogrel for major bleeding at 30 days (750 participants in 4 studies, very low quality evidence) and major bleeding at 1 year (8135 participants in 3 studies, low quality evidence) for STEMI with revascularisation.
- There was a clinically important increase in minor bleeding at 30 days (750 participants in 4 studies, low quality evidence) when ticagrelor was compared to clopidogrel. There was however no clinically important difference between ticagrelor and clopidogrel for minor bleeding at 1 year (8313 participants in 3 studies, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for stroke at 30 days (318 participants in 2 studies, very low quality evidence) and stroke at 1 year (8630 participants in 4 studies, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and clopidogrel for need for revascularisation at 30 days (442 participants in 2 studies, low quality evidence). There was however a clinically important difference between ticagrelor and clopidogrel for need for revascularisation at 1 year (1140 participants in 3 studies, moderate quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for stent thrombosis (definite or probable) at 30 days (174 participants in 1 study, low quality

evidence). There was however no clinically important difference between ticagrelor and clopidogrel for stent thrombosis (type not specified) at 1 year (644 participants in 2 studies, very low quality evidence) and stent thrombosis (definite and probable) at 1 year (7544 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was a clinically important increase in breathing adverse effects at 30 days (318 participants in 2 studies, low quality evidence) and at 1 year (7471 participants in 1 study, moderate quality evidence) when ticagrelor was compared to clopidogrel for STEMI with revascularisation.
- There was a clinically important increase in bradycardiac adverse effects at 30 days (318 participants in 2 studies, very low quality evidence) when ticagrelor was compared to clopidogrel. There was however no clinically important difference between ticagrelor and clopidogrel for bradycardiac adverse effects at 1 year (7715 participants in 2 studies, low quality evidence) for STEMI with revascularisation.
- There was a clinically important increase in other adverse effects at 30 days (418 participants in 3 studies, low quality evidence) when ticagrelor was compared to clopidogrel. There was however no clinically difference between ticagrelor and clopidogrel for other adverse effects at 1 year (7471 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor compared to clopidogrel for unplanned urgent readmission at 30 days (144 participants in 1 study, very low quality evidence) for STEMI with revascularisation.

Prasugrel versus clopidogrel

ACS with/without revascularisation

- There was a clinically important benefit of prasugrel compared to clopidogrel for all-cause mortality at 30 days (13142 participants in 4 studies, low quality evidence). There was however no clinically important difference between prasugrel and clopidogrel for all-cause mortality at 1 year (15126 participants in 3 studies, moderate quality evidence) for ACS with/without revascularisation.
- There was a clinically important benefit of prasugrel compared to clopidogrel for cardiac mortality at 30 days (13049 participants in 3 studies, low quality evidence) and at 1 year (15051 participants in 2 studies, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for re-infarction at 30 days (13111 participants in 4 studies, low quality evidence). There was however a clinically important benefit of prasugrel when compared to clopidogrel for re-infarction at 1 year (15051 participants in 3 studies, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for major bleeding at 30 days (12994 participants in 3 studies, very low quality evidence) and at 1 year (14900 participants in 2 studies, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for minor bleeding at 30 days (3754 participants in 2 studies, very low quality evidence) and at 1 year (1443 participants in 1 study, low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for stroke at 30 days (13049 participants in 3 studies, very low quality evidence) and at 1 year (15126 participants in 3 studies, very low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for need for revascularisation at 30 days (3723 participants in 2 studies, low quality evidence) and

at 1 year (13683 participants in 2 studies, low quality evidence) for ACS with/without revascularisation.

- There was no clinically important difference between prasugrel and clopidogrel for stent thrombosis (type not specified) at 30 days (282 participants in 2 studies, very low quality evidence) and stent thrombosis (definite or probable) at 1 year (15051 participants in 2 studies, moderate quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for other adverse effects at 30 days (282 participants in 2 studies, very low quality evidence) and at 1 year (14900 participants in 2 studies, very low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for unplanned urgent readmission at 30 days (189 participants in 1 study, very low quality evidence) and at 1 year (1443 participants in 1 study, very low quality evidence) for ACS with/without revascularisation.

UA/NSTEMI with/without revascularisation

With revascularisation

- There was no clinically important difference between prasugrel and clopidogrel for cardiac mortality at 1 year (10074 participants in 1 study, low quality evidence) for UA/NSTEMI with revascularisation.
- There was a clinically important benefit of prasugrel compared to clopidogrel for re-infarction at 1 year (10074 participants in 1 study, low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for major bleeding at 1 year (9981 participants in 1 study, low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for stroke at 1 year (10074 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for stroke at 1 year (9326 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation in people aged <75 years.

Without revascularisation

- There was a clinically important benefit of prasugrel compared to clopidogrel for all-cause mortality at 30 days (9326 participants in 1 study, low quality evidence) for UA/NSTEMI without revascularisation.
- There was a clinically important benefit of prasugrel compared to clopidogrel for cardiac mortality at 30 days (9326 participants in 1 study for UA/NSTEMI without revascularisation
- There was no clinically important difference between prasugrel and clopidogrel for cardiac mortality at 1 year (9326 participants in 1 study, very low quality evidence) for UA/NSTEMI without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for re-infarction at 30 days (9326 participants in 1 study, very low quality evidence) for UA/NSTEMI with revascularisation in people aged <75 years.
- There was no clinically important difference between prasugrel and clopidogrel for re-infarction at 1 year (9326 participants in 1 study, low quality evidence) for UA/NSTEMI without revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for major bleeding at 30 days (9240 participants in 1 study, low quality evidence) for UA/NSTEMI without revascularisation

- There was no clinically important difference between prasugrel and clopidogrel for stroke at 30 days (9326 participants in 1 study, low quality evidence) for UA/NSTEMI without revascularisation
- There was no clinically important difference between prasugrel and clopidogrel for health-related quality of life (measures: EQ5D, SAQ Physical, SF-12 physical, SF-12 mental, SF-36) at 1 year (1774-5764 participants in 1 study, moderate quality evidence) for UA/NSTEMI without revascularisation.

STEMI with revascularisation

- There was a clinically important benefit of prasugrel compared to clopidogrel for all-cause mortality at 30 days (3596 participants in 2 studies, low quality evidence) and all-cause mortality at 1 year (3534 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of prasugrel compared to clopidogrel for cardiac mortality at 30 days (3534 participants in 1 study, low quality evidence) and cardiac mortality at 1 year (3534 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was however a clinically important benefit of prasugrel when compared to clopidogrel for re-infarction at 30 days (3596 participants in 2 studies, low quality evidence) and at 1 year (3534 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for major bleeding (3534 participants in 1 study, very low quality evidence) and bleeding (major and minor) at 30 days (62 participants in 1 study, low quality evidence) and at 1 year (3534 participants in 1 study, very low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for minor bleeding at 30 days (3534 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for stroke at 30 days (3534 participants in 1 study, low quality evidence) and at 1 year (3534 participants in 1 study, very low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for need for revascularisation at 30 days (3534 participants in 1 study, low quality evidence) and at 1 year (3534 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between prasugrel and clopidogrel for stent thrombosis (definite or probable) at 30 days (3534 participants in 1 study, low quality evidence), stent thrombosis (type not specified) and 30 days (62 participants in 1 study, very low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit for prasugrel compared to clopidogrel for other adverse effects at 30 days (62 participants in 1 study, low quality evidence) for STEMI with revascularisation.

Ticagrelor versus prasugrel

ACS with/without revascularisation

- There was a clinically important harm in all-cause mortality at 30 days (1698 participants in 6 studies, low quality evidence) and at 1 year (4018 participants in 1 study, low quality evidence) when ticagrelor was compared to prasugrel for ACS with/without revascularisation.
- There was a clinically important benefit of ticagrelor when compared to prasugrel for cardiac mortality at 30 days (1543 participants in 3 studies, low quality evidence). There was however a clinically important harm in cardiac mortality at 1 year (4018 participants

in 1 study, very low quality evidence) when ticagrelor was compared to prasugrel for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for re-infarction at 30 days (1430 participants in 4 studies, very low quality evidence). There was however a clinically important harm in re-infarction at 1 year (4018 participants in 1 study, low quality evidence) when ticagrelor was compared with prasugrel for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for major bleeding at 30 days (1698 participants in 6 studies, very low quality evidence) and at 1 year (3762 participants in 1 study, very low quality evidence) for ACS with/without revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stroke at 30 days (1593 participants in 4 studies, very low quality evidence) and at 1 year (4018 participants in 1 study, very low quality evidence) for ACS with/without revascularisation.

UA/NSTEMI with revascularisation

- There was a clinically important benefit of ticagrelor compared to prasugrel for all-cause mortality at 30 days (313 participants in 2 studies, very low quality evidence) for UA/STEMI with revascularisation for UA/STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor when compared to prasugrel for cardiac mortality at 30 days (313 participants in 2 studies, low quality evidence) for UA/STEMI with revascularisation.
- There was a clinically important benefit of ticagrelor when compared to prasugrel for re-infarction at 30 days (100 participants in 1 study, low quality evidence) for UA/STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for major bleeding at 30 days (313 participants in 2 studies, very low quality evidence) for UA/STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stroke at 30 days (313 participants in 2 studies, low quality evidence) for UA/STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stent thrombosis (definite or probable) at 1 year (4018 participants in 1 study, very low quality evidence) for UA/STEMI with revascularisation.

STEMI with revascularisation

- There was a clinically important benefit of ticagrelor compared to prasugrel for all-cause mortality at 30 days (1385 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was a clinically important benefit of prasugrel when compared to ticagrelor for cardiac mortality at 30 days (1230 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for re-infarction at 30 days (1330 participants in 3 studies, very low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for major bleeding at 30 days (1385 participants in 4 studies, very low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for minor bleeding at 30 days (1385 participants in 4 studies, very low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stroke at 30 days (1280 participants in 2 studies, very low quality evidence) for STEMI with revascularisation.

- There was no clinically important difference between ticagrelor and prasugrel for need for revascularisation at 30 days (1230 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stent thrombosis (definite) at 30 days (1230 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for stent thrombosis (type not specified) at 30 days (100 participants in 2 studies, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for breathing adverse effects at 30 days (50 participants in 1 study, low quality evidence) for STEMI with revascularisation.
- There was no clinically important difference between ticagrelor and prasugrel for bradycardic adverse effects at 30 days (50 participants in 1 study, very low quality evidence) for STEMI with revascularisation.
- There was a clinically important harm in other adverse effects at 30 days (139 participants in 3 studies, very low quality evidence) when ticagrelor was compared with prasugrel for STEMI with revascularisation.

Network meta-analyses

All-cause mortality at 30 days

- Fourteen studies were included in the network; prasugrel and ticagrelor may both be more effective than clopidogrel in reducing the risk of mortality. Prasugrel may be more effective than ticagrelor. However, there was uncertainty in the network. No inconsistency was identified.
-

New MI at 30 days

- Eleven studies were included in the network; ticagrelor is more effective than clopidogrel in reducing the risk of MI. Prasugrel may be more effective than clopidogrel. Ticagrelor may be more effective than prasugrel. However, there was uncertainty in the network. No inconsistency was identified.

Stroke at 30 days

- Eight studies were included in the network; prasugrel may be more effective than clopidogrel and ticagrelor in reducing the risk of stroke. Clopidogrel may also be more effective than ticagrelor. However, there was uncertainty in the network. No inconsistency was identified.
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Major bleeding at 30 days

- Ten studies were included in the network; no clinical difference between the three treatments in terms of reducing the risk of major bleeding. However, there uncertainty in the network. No inconsistency was identified.

Minor bleeding at 30 days

- Ten studies were included in the network; prasugrel is more effective than clopidogrel and ticagrelor in reducing the risk of minor bleeding. Clopidogrel may also be more effective than ticagrelor. However, there was uncertainty in the network. Evidence of inconsistency was identified due to one study.

1.7.2 Health economic evidence statements

- One cost-utility analysis found that for:
    - People with ACS managed medically or invasively ticagrelor was cost effective compared to clopidogrel (ICER: £3,805 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
    - People with ACS undergoing PCI ticagrelor was cost effective compared to prasugrel (ICER: £3,482 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that ticagrelor was cost effective compared to clopidogrel for people with ACS managed medically (ICER: £2,925 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that for people with ACS undergoing PCI prasugrel was cost effective compared to clopidogrel:
    - for treating people with STEMI with diabetes (ICER: £1,732 per QALY gained).
    - for treating people with STEMI and without diabetes (ICER: £7,073 per QALY gained)
    - for treating people with UA/NSTEMI with diabetes prasugrel was dominant (less costly and more effective)
    - for treating people with UA/NSTEMI without diabetes (ICER: £4,154 per QALY gained).

  This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that ticagrelor was cost effective compared to prasugrel and clopidogrel for treating people with ACS undergoing PCI (ICER: £6,556 per QALY gained compared to clopidogrel). It also found that prasugrel was extendedly dominated by ticagrelor. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-utility analysis found that ticagrelor was cost effective compared to prasugrel and clopidogrel for treating people with ACS undergoing PCI (ICER: £6,210 per QALY gained compared to prasugrel). This analysis was assessed as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that for treating people with STEMI:
    - When 1-year treatment effects were based on studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel, ticagrelor was cost effective compared to prasugrel and clopidogrel (ICERs: £3,507 per QALY gained prasugrel compared to clopidogrel; £7,455 per QALY gained ticagrelor compared to prasugrel).
    - When 1-year treatment effects were based on studies comparing prasugrel to clopidogrel and ticagrelor to prasugrel, prasugrel was cost effective compared to clopidogrel (ICER: £3,615 per QALY gained) and prasugrel was dominant compared to ticagrelor (less costly and more effective).
    - When 1-year treatment effects were based on studies comparing ticagrelor to clopidogrel and ticagrelor to prasugrel, prasugrel was cost effective compared to clopidogrel (ICER: £2,469 per QALY gained) and prasugrel was dominant compared to ticagrelor (less costly and more effective).
- The same original cost-utility analysis found that for treating people with UA/NSTEMI:
    - When 1-year treatment effects were based on studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel, ticagrelor was cost effective compared to prasugrel and clopidogrel (ICERs: £10,424 per QALY gained ticagrelor compared to prasugrel; £4,510 per QALY gained prasugrel compared to clopidogrel). .
    - When 1-year treatment effects were based on studies comparing prasugrel to clopidogrel and ticagrelor to prasugrel, prasugrel was cost effective compared to clopidogrel (ICER: £4,525 per QALY gained) and prasugrel was dominant compared to ticagrelor (less costly and more effective).

- When 1-year treatment effects were based on studies comparing ticagrelor to clopidogrel and ticagrelor to prasugrel, prasugrel was cost effective compared to clopidogrel (ICER: £1,979 per QALY gained) and prasugrel was dominant compared to ticagrelor (less costly and more effective).

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee agreed that outcomes critical for decision making included: mortality up to 30 days and 1 year (all-cause and cardiac); re-infarction up to 30 days and 1 year; complications related to bleeding; and health-related quality of life. While the focus of the evidence review was on initial antiplatelet therapy, the committee considered the one year time-point for these outcomes to be more critical than up to 30 days. Stroke, need for revascularisation, stent thrombosis, adverse effect of breathlessness, bradycardia, other adverse effects and unplanned urgent readmission within 30 days for any reason were also considered important outcomes.

For the comparison of ticagrelor versus clopidogrel in people with ACS, evidence was reported for all critical and important outcomes (at up to 30 days and one year) except for health-related quality of life. The committee noted that not all 30-day outcomes were available from the largest study in this comparison (Wallentin, 2009; PLATO).

For the comparison of prasugrel versus clopidogrel in people with ACS, evidence was reported for all critical and important outcomes (at up to 30 days and up to one year) except for the adverse events of breathlessness and bradycardia, and unplanned urgent readmission within 30 days. The committee noted that not all 30-day outcomes were available from the two largest studies in this comparison (Wiviott, 2007; TRITON).

For the comparison of ticagrelor versus prasugrel in people with ACS, evidence was reported at up to 30 days/ 1 month for all outcomes except health-related quality of life and unplanned urgent readmission within 30 days. There was 1 year data available for all-cause mortality, cardiac mortality, stroke, re-infarction, major bleeding and stent thrombosis (definite and probable). The committee noted that 30-day outcomes were not available from the largest study in this comparison (ISAR-REACT 5).

For the purposes of this review, bleeding scores were considered 'major' or 'minor' according to author and bleeding scale definitions. Where studies reported bleeding on multiple scales, the most relevant available scale was used in the meta-analysis based on a hierarchy as per the protocol. Stent thrombosis was included in the analyses if it was reported as 'definite and/or probable', as reported in studies. Outcome data which were not reported as definite or probable stent thrombosis were included but analysed separately.

1.8.1.2 The quality of the evidence

The quality (certainty) of the evidence ranged from a GRADE rating of very low to moderate. The main reasons for downgrading the quality of the evidence were risk of bias, imprecision and inconsistency. The presence of selection bias in terms of lack of adequate randomisation and allocation concealment commonly resulted in a high or very high risk of bias rating but this is unlikely to have systematically favoured one intervention over the other.

1.8.1.3 Benefits and harms

The committee considered the evidence (network meta-analyses (NMAs) and pairwise meta-analyses) for the following comparisons in people with ACS: ticagrelor versus clopidogrel; prasugrel versus clopidogrel; ticagrelor versus prasugrel. The evidence included populations of overall ACS with or without revascularisation for the pairwise meta-analyses and NMAs.

All ACS are believed to share the same basic pathophysiology in terms of acute atherosclerotic plaque rupture leading to acute thrombus formation and compromise of coronary blood flow. For this reason, analysing the effects of anti-platelet therapy on all ACS grouped together should be a satisfactory way of evaluating differential efficacy of different therapeutic strategies. The committee also noted the many similarities in treatment of STEMI and UA/NSTEMI populations. However, STEMI is a medical emergency requiring immediate treatment, and given the well established differential onsets of action of clopidogrel, prasugrel and ticagrelor it is conceivable that this may impact their relative clinical effectiveness in STEMI patients compared to UA/NSTEMI. Moreover, whereas the majority of people with STEMI will proceed to angiography with the intention of performing PCI, a greater proportion of people with UA/NSTEMI are managed medically. Existing subgroup data in STEMI patients have also suggested that the benefits of prasugrel and ticagrelor over clopidogrel may not be as large as those seen in the overall ACS population. For these reasons, the committee wanted to examine the relative effects of clopidogrel, prasugrel and ticagrelor separately in the STEMI and UA/NSTEMI populations where trial data permitted this to be evaluated, considering substrata comparisons by condition (i.e. STEMI or UA/NSTEMI) and management approach (i.e. with or without revascularisation).

Additionally, the presence of imprecision in some of the pairwise outcome results made interpretation of the clinical benefit or harm associated with interventions challenging. However, the imprecision was predominantly in the pairwise meta-analyses for the individual subpopulations. The committee were satisfied that they could have more confidence in the results for the overall ACS population. The discussion below therefore represents the evidence from the all ACS analyses. The discussion has however been split into people that receive PCI and those who do not as prasugrel is not licensed in those that do not and so the potential treatment options differ.

People undergoing PCI

In people undergoing PCI, dual antiplatelet therapy could be aspirin plus one of clopidogrel, prasugrel or ticagrelor. As discussed above, the committee considered the analyses using all ACS data combined to be the most informative as relative treatment effects were likely to be consistent and this will reduce imprecision. The evidence discussed below is therefore from the all ACS analyses.

Network meta-analyses

The committee reviewed outcome data at two timepoints, 30 days and 1 year, and agreed that NMAs should be conducted if there was sufficient evidence to do so.

There was sufficient evidence to conduct NMAs on all ACS for five outcomes at 30 days (all-cause mortality, new myocardial infarction, stroke, major bleeding and minor bleeding). The committee agreed that these outcomes are appropriate for aiding decision-making by demonstrating the clinical effectiveness of these drugs and their safety. Following the publication of the ISAR REACT-5 trial it became technically possible to do NMAs for the 1 year outcome data. However, checks prior to conducting NMAs identified inconsistencies which would have produced unreliable results and accordingly a 1 year NMA was not performed (see NMA document for more information).

The 30 day NMA results (relative risks, treatment ranks, probability of the outcome occurring and probability of the treatment being the best) were presented to the committee. The all-

cause mortality network was the largest informed by 14 studies, the new myocardial infarction network was informed by 11 studies, the stroke network was informed by 8 studies and the bleeding networks (major and minor) were both informed by 10 studies. The NMA results suggest that prasugrel and ticagrelor are more clinically effective than clopidogrel for the outcomes all-cause mortality and new myocardial infarction. The stroke data showed prasugrel to be the most beneficial agent and ticagrelor the least, but confidence intervals were wide and the committee regarded this outcome with caution. For the outcome of major bleeding there was no clear clinical difference between the three treatments. However, the NMA results indicate that prasugrel may be more clinically effective than clopidogrel and ticagrelor respectively in terms of minimising minor bleeding events. Overall the committee agreed that clopidogrel is the least clinically effective treatment option, with mixed results for prasgurel versus ticagrelor, favouring prasugrel but with sufficient uncertainty in the networks to clearly distinguish which treatment is more clinically effective (further details can be found in the NMA document).

Pairwise meta-analyses

The committee reviewed the pairwise meta-analyses for the outcome data reported at 30 days that was not included in the NMAs and pairwise meta-analysis outcome data at 1 year.

Ticagrelor versus clopidogrel

Evidence from the pairwise meta-analysis for the comparison of ticagrelor versus clopidogrel showed clinical benefit of ticagrelor for the outcome of all-cause mortality and re-infarction at 1 year, and at both 30 days and 1 year when considering the need for revascularisation. Ticagrelor also reduced stent thrombosis events, but only at 1 year. For cardiac mortality, the evidence showed that clopidogrel is more effective in reducing events at 30 days only, with clinical benefit of ticagrelor at 1 year. Clopidogrel caused fewer breathing adverse events than ticagrelor at 30 days and 1 year. Breathing adverse effects, associated more often with ticagrelor, were considered by the committee to be reversible in most cases. However, the committee highlighted the difficulty in capturing evidence for those patients who discontinue drug treatment due to side effects such as breathlessness, and then subsequently experience cardiac events. There was no clinical difference between the two treatments for bleeding outcomes (major bleeding and minor bleeding) and stroke at 1 year.

Prasugrel versus clopidogrel

Evidence for the comparison of prasugrel versus clopidogrel showed clinical benefit of prasugrel for the outcomes of cardiac mortality and re-infarction at 1 year. There was no clinical difference between the two treatments for stent thrombosis (at 30 days and 1 year) and for the following outcomes at 1 year: all-cause mortality, major bleeding, minor bleeding, stroke, need for revascularisation, stent thrombosis, health-related quality of life, adverse effects and readmission.

Ticagrelor versus prasugrel

When ticagrelor was compared with prasugrel, the pairwise evidence suggested that prasugrel is more clinically effective in the long-term (up to 1 year) in terms of all-cause mortality, cardiac mortality and re-infarction. However, most of these differences were relatively small and, as already noted, the quality assessment showed uncertainty for several of the outcome measures. The committee agreed there was no clinically important difference between the two treatments for major bleeding, stroke, stent thrombosis and adverse effects (at 30 days and 1 year).

Discussion

The committee noted and discussed additional uncertainty in the evidence due to inconsistency in the indirect and direct clinical evidence at 1 year. As described above ideally

NMA would be used to bring together all the evidence at 1 year into a single set of consistent treatment effects. However, due to significant inconsistency between direct and indirect effects NMA was considered unreliable and was not undertaken. Inconsistency was identified in 3 of 4 outcomes (no data was available for ticagrelor versus prasugrel for minor bleeding) between the direct and indirect estimates of relative treatment effect. For example, using the data for prasugrel and ticagrelor each compared to clopidogrel generated an odds ratio for ticagrelor versus prasugrel of 0.77 (0.61 to 0.97) which favours ticagrelor but the direct evidence from ISAR-REACT 5 gave an odds ratio of 1.24 (0.90 to 1.70) which favours prasugrel. The odds ratio for reinfarction was implicitly 1.08 (0.92 to 1.27) using indirect data but was 1.63 (1.17 to 2.26) using the direct comparison from ISAR-REACT 5, both favouring prasugrel; and for major bleeding was implicitly 0.73 (0.57 to 0.93) for the indirect comparison where the direction of effect favours ticagrelor and 1.06 (0.78 to 1.44) in the direct evidence where the direction of effect favours prasugrel. Stroke was not found to be inconsistent with 1.22 (0.80 to 1.84) indirect and 1.16 (0.62 to 2.14) direct. While being aware of some differences between trials, the committee could not determine a clear explanation for the inconsistency.

Given the lack of an NMA to bring all data together, the committee considered whether particular evidence was more relevant to decision making than others. They noted that the data for ticagrelor and prasugrel compared with clopidogrel included some very large trials that were considered important parts of the evidence base. However, they also agreed that the 1 year evidence that directly compared these drugs from ISAR-REACT 5 was the most relevant in terms of understanding whether there were differences in sustained clinical effects between prasugrel and ticagrelor. The committee discussed ISAR-REACT 5 in detail. Aspects of ACS management can vary between countries (such as use of radial versus femoral approach for PCI, or other such specifics) and it was noted that this study was not carried out in the UK. The committee discussed if this raised any issues for interpretation in a UK context. They agreed that for STEMI the evidence was directly applicable. However the committee noted that the time to angiography for people with UA/NSTEMI in the study was much shorter than is currently achieved in the UK. Given that prasugrel is only given at the time of PCI the committee agreed this made them less confident in the generalisability of the study to UK practice for UA/NSTEMI.

Net health gains

Health economic modelling undertaken for the guideline assessed overall health gain in terms of QALYs (taking into account both benefits and harms due to death, re-infarction, stroke, major bleeding and minor bleeding). The treatment option that resulted in the highest QALYs in the analysis varied between prasugrel and ticagrelor depending on which clinical data was used in the model, showing that the inconsistency identified in the evidence for individual outcomes leads to overall uncertainty in terms of net health gain. When ISAR-REACT 5 was incorporated prasugrel had the highest QALYs but when it was not used (and data from studies comparing ticagrelor or prasugrel to clopidogrel were used) ticagrelor had the highest QALYs. These results are discussed further in the next section about cost effectiveness.

Conclusions

Overall the committee agreed that the clinical evidence supported the use of ticagrelor and prasugrel over clopidogrel. In most cases there was not clear evidence of clinical differences between ticagrelor and prasugrel although where there was evidence it generally favoured prasugrel, exceptions being the indirect comparisons of ticagrelor and prasugrel using studies that compared each to clopidogrel which suggest benefits for ticagrelor over prasugrel in terms of mortality and major bleeding. The committee however agreed that the most pertinent evidence about the relative treatment effects of prasugrel versus ticagrelor came from the ISAR-REACT 5 study that compared them head to head and reported 1 year outcomes. The committee were satisfied this was applicable to the UK setting for people with

STEMI. They agreed this was probably applicable for people with UA/NSTEMI undergoing PCI as well but noted that as the time to angiography (and so PCI) for people with UA/NSTEMI was much shorter than typical in the UK and prasugrel isn't given until the time of PCI and this introduced some additional uncertainty in this subpopulation.

People not undergoing PCI

In people not undergoing PCI, prasugrel is not an option and so the committee considered the evidence for ticagrelor versus clopidogrel. As discussed above, the committee considered the analyses using all ACS data combined to be the most informative as relative treatment effects were likely to be consistent and this will reduce imprecision. The evidence discussed below is therefore from the all ACS analyses.

Taking into account the evidence from the NMA and pairwise meta-analyses described above the committee concluded that there was evidence of clinical benefit with ticagrelor versus clopidogrel in terms of all-cause mortality, cardiac mortality and reinfarction. This was generally seen at 30 days and 1 year. There was some uncertainty in all-cause mortality at 30 days as the confidence interval crossed 1. In addition, cardiac mortality in the overall ACS population at 30 days did not show a benefit for ticagrelor, but there was considerable imprecision around this estimate and it was inconsistent with all other mortality analyses. Evidence also showed a clinical benefit of ticagrelor at both 30 days and 1 year in the need for revascularisation, and evidence for reduced stent thrombosis events at 1 year.

The committee agreed that the evidence overall did not demonstrate a clinically important harm with ticagrelor over clopidogrel in terms of major bleeding, minor bleeding or stroke at 30 days or 1 year. Minor bleeding was increased somewhat with ticagrelor but the committee agreed that minor bleeding would typically not lead to any long term health problems. In addition, in the NMA 30 day analysis there was uncertainty in the treatment effect as the confidence interval crossed 1. The committee noted that in the 30 day NMA and in the 1 year meta-analysis stroke was higher with ticagrelor than clopidogrel and that stroke was a significant adverse outcome with long term health consequences, but absolute differences in number of events was small and confidence intervals were wide and so the committee regarded this outcome with caution and did not consider there to be clear evidence of harm.

Clopidogrel caused fewer breathing adverse events than ticagrelor at 30 days and 1 year. These were considered by the committee to be reversible in most cases and so were not likely to have a substantial impact on health long term. However, the committee highlighted the difficulty in capturing evidence for those patients who discontinue drug treatment due to side effects such as breathlessness, and then subsequently experience cardiac events.

Cost-utility analyses (that took account of both benefits and harms due to death, re-infarction, stroke and bleeding) found an overall increase in QALYs with ticagrelor compared to clopidogrel. This included one analysis in people with ACS intended for non-invasive treatment.

Given the above, the committee concluded that the clinical evidence supported the use of ticagrelor over clopidogrel and that ticagrelor was the most clinically effective option in people not undergoing PCI where only clopidogrel and ticagrelor are the treatment options. The data is dominated by people with UA/NSTEMI because far fewer people with STEMI are managed without PCI, but the committee felt that the conclusions could be extrapolated to STEMI since the basic pathophysiology of NSTEMI and STEMI is almost identical and they considered the superiority of ticagrelor over clopidogrel in the non-PCI population as a whole to be clearcut. However, they noted that clinical studies in this area often exclude older or more high risk people and that these people may be at greater risk of bleeding. Given that some of the evidence suggested ticagrelor may increase bleeding they agreed that, in people at high risk of bleeding, harms might outweigh benefits and so agreed that either clopidogrel plus aspirin or aspirin alone may be more appropriate to use in this group. They agreed with

the conclusion of the previous guideline committee, that those who are at higher bleeding risk are hard to define precisely but should be identified based on clinical assessment taking into account a range of factors including age and frailty.

1.8.2 Cost effectiveness and resource use

Five published economic evaluations were included for this review including the analyses that informed the most recent technology appraisal guidance for prasugrel and ticagrelor. These varied in terms of what comparators were included and what ACS population they related to. In additional new economic modelling was undertaken for this guideline update.

Two UK analyses compared ticagrelor and clopidogrel, one that informed the ticagrelor TA236 in an ACS population (invasive and non-invasive management; analysed overall and for NSTEMI, STEMI and UA/NSTEMI separately) and the other in people with ACS intended for non-invasive therapy. In both these analyses ticagrelor was found to be cost effective compared to clopidogrel with an incremental cost effectiveness ratio around £3,000 to £5,000 per QALY gained. Ticagrelor had higher costs and QALYs than clopidogrel. Both analyses were based on treatment effect data from the PLATO RCT. The committee discussed the additional studies comparing ticagrelor and clopidogrel that were identified in the review of clinical effectiveness evidence undertaken for the guideline, but it was noted that PLATO is by far the largest trial comparing ticagrelor and clopidogrel and effect sizes from the guideline meta-analysis that incorporated all available evidence were mostly similar to the PLATO study alone. The committee also discussed whether the baseline risks in the economic analysis of people intended for non-invasive therapy may be lower than in the real world as the average age in the subpopulation used in the analysis appeared lower than they would expect. However, the committee concluded that for people being medically managed, where prasugrel is not an option, the evidence supported ticagrelor being the most cost-effective option (over clopidogrel) despite being higher cost, due to the greater health benefits from use of ticagrelor.

For people with ACS undergoing PCI, prasugrel is also a treatment option. The UK analysis that informed the prasugrel NICE TA317 guidance found prasugrel to be cost effective compared to clopidogrel in an ACS population undergoing PCI (analysed for STEMI and NSTEMI, with and without diabetes, separately), with results varying from dominant to an incremental cost effectiveness ratio of £7,000 per QALY gained. This was based on the TRITON-TIMI 38 RCT which was included in the clinical evidence review. The committee discussed the additional studies comparing prasugrel and clopidogrel that were identified in the review of clinical effectiveness evidence undertaken for the guideline, but it was noted that TRITON-TIMI 38 is by far the largest trial comparing prasugrel and clopidogrel and effect sizes from the guideline meta analysis that incorporated all available evidence were mostly similar, although the mortality treatment effect was slightly more favourable in the TRITON-TIMI 38 trial. However, in order to determine which of the three DAPT options is most cost effective in an ACS PCI population an analysis including clopidogrel, prasugrel and ticagrelor together is required.

As part of the analysis that informed the ticagrelor TA236, a comparison of ticagrelor and prasugrel was also undertaken in an ACS population managed invasively. It was based on an indirect comparison of ticagrelor and prasugrel using the PLATO and TRITON-TIMI 38 trials that compared each to clopidogrel. This analysis found that ticagrelor had higher costs and QALYs compared to prasugrel and was the most cost-effective option with an ICER of £3,482 per QALY gained. Although this was noted at the time of the technology appraisal, they chose not to recommend ticagrelor over prasugrel.

Two published economic evaluations compared ticagrelor, prasugrel and clopidogrel in an ACS population undergoing PCI. One took a Canadian cost perspective and was based on three randomised controlled trials (PLATO, TRITON-TIMI 38 and DISPERSE 2). The other used a Norwegian cost perspective and was based on two randomised controlled trials

(PLATO and TRITON-TIMI 38). Both analyses found that ticagrelor had the highest costs and QALYs followed by prasugrel and then clopidogrel. However, ticagrelor was also the most cost-effective option in both analyses. The committee agreed that there were a number of limitations of these analyses, in particular that they do not take into account all the currently available clinical effectiveness evidence including new head-to-head data for ticagrelor and prasugrel.

After reviewing the published clinical and cost effectiveness evidence, the committee considered there to be uncertainty about which intervention was the most cost-effective option for people undergoing PCI in the NHS setting and prioritised this area for new analysis as part of the development of the guideline. A decision analytic model was constructed to compare ticagrelor, prasugrel and clopidogrel in people with STEMI and UA/NSTEMI undergoing PCI from a UK NHS perspective. Relative treatment effects were based on the systematic review and meta-analyses undertaken as part of this guideline update. STEMI and UA/NSTEMI were modelled separately as baseline risks were considered likely to be different, although relative treatment effects were assumed to be the same. Relative treatment effects in the model were based on the 30 day network meta-analysis as this combines all available data into a single set of consistent treatment effects and the 1 year pair-wise meta-analyses. As described above, network meta-analysis of the 1 year data was considered unreliable as there was inconsistency in the network. This means that treatment effects within the evidence network are not consistent with each other and using different data may lead to different conclusions. The model was therefore run using different combinations of the available pairwise data to explore whether this would impact conclusions – this resulted in 3 treatment effect data scenarios in the analysis.

In the base case analysis, the DAPT option that was most cost effective varied depending on the clinical data used to inform the 1 year relative treatment effects. Ticagrelor was the most cost effective DAPT option, for STEMI and UA/NSTEMI, when data from studies comparing prasugrel to clopidogrel and ticagrelor to clopidogrel (and not ISAR-REACT 5) were used to inform the relative treatment effects at 1 year in the model (data scenario 1). Prasugrel was the most cost effective DAPT option for both STEMI and UA/NSTEMI when data comparing ticagrelor and prasugrel from ISAR-REACT 5 were incorporated (data scenarios 2 and 3). . Ticagrelor had the highest costs in all scenarios and ACS subgroups but only had the highest QALYs in scenario 1. Prasugrel had higher QALYs and lower costs than ticagrelor in scenarios 2 and 3. Clopidogrel had the lowest costs in all scenarios but was not the most cost effective option in any scenario.

It was noted that scenario 2 (in which meta-analysed data from studies comparing prasugrel to clopidogrel and the ISAR-REACT 5 trial that compared ticagrelor to prasugrel were used to inform the relative treatment effects at 1 year in the model) resulted in ticagrelor being ranked the 3rd most cost-effective option for both STEMI and UA/NSTEMI, as it resulted in having fewer QALYs than clopidogrel. This was because using the prasugrel versus clopidogrel data combined with the prasugrel versus ticagrelor data made ticagrelor slightly worse on certain outcomes, for example, the resulting odds ratio for mortality for ticagrelor versus clopidogrel was 1.24. The committee noted that this was inconsistent with the studies that directly compared ticagrelor with clopidogrel (such as PLATO) and were concerned that excluding data from PLATO from the treatment effects was not ideal as this trial was large, closely applicable to UK practice, and recruited in the UK. Therefore, despite these results they agreed that clopidogrel was the least cost effective option.

The committee discussed the difference in conclusions about cost effectiveness between the different data scenarios analysed and how this was due to the inconsistency seen in the 1 year clinical data. As discussed in the ‘Benefits and harms’ section above all three scenarios utilised key clinical studies in the area and it was not clear what might be causing the inconsistency. However, as also described above, the main uncertainty in practice was agreed to be between ticagrelor and prasugrel and studies directly comparing these agents were best placed to address this. More weight was therefore given by the committee to the

scenarios incorporating ISAR-REACT 5 in terms of determining whether ticagrelor or prasugrel was the most cost effective, although the issue about the generalisability to a UK UA/NSTEMI population, described above, were also taken into account.

The committee discussed the results of the sensitivity analysis where an additional treatment effect was included in the clopidogrel group to reflect rivaroxaban use as an adjunctive therapy in post-ACS patients (as covered in NICE TA335). Use of rivaroxaban for this indication is not currently licensed for use with ticagrelor and prasugrel. When rivaroxaban was assumed to be used in all people receiving clopidogrel, clopidogrel (incorporating rivaroxaban) became the most cost effective option in scenario 1 and 2; prasugrel remained the most cost effective option in scenario 3. However, conclusions did not differ from the base case analyses when rivaroxaban usage was assumed to be 1.8% (as was estimated current practice among people receiving clopidogrel). Given making recommendations about rivaroxaban use is outside the scope of this update the analysis with current practice usage was considered the most relevant. It was also highlighted at consultation that some recent studies have combined rivaroxaban with prasugrel and ticagrelor, but the use of rivaroxaban was not part of this guideline update and so this issue was not examined by the committee. The committee noted practice would not be greatly impacted if a recommendation for ticagrelor or prasugrel was made, as only a small proportion of people with ACS are prescribed rivaroxaban alongside clopidogrel.

Summary Conclusions

People with STEMI with PCI

For STEMI in scenario 1, ticagrelor was the most cost-effective treatment with low uncertainty within that scenario but in both scenario 2 and scenario 3 prasugrel was the most cost-effective, with higher QALYs, dominating ticagrelor and being the most cost-effective in 58% and 96% of simulations respectively. Scenarios 2 and 3 were largely influenced by the results from ISAR-REACT 5, and the committee agreed that this trial is reflective of how the STEMI population would be treated in the UK. Also, before the publication of ISAR-REACT 5, the committee were confident that there was evidence to show that ticagrelor and prasugrel were both more effective than clopidogrel but there was limited evidence directly comparing the effectiveness of prasugrel and ticagrelor. It was therefore agreed that the publication of ISAR-REACT 5 addressed the uncertainty around the relative effectiveness of ticagrelor and prasugrel showing that, although there are no major differences in either benefit or harm between prasugrel and ticagrelor, where there was evidence of difference it favoured prasugrel. The cost-effectiveness analysis further supported the use of prasugrel when this study was incorporated. As a result, the committee had confidence that prasugrel should be recommended in people with STEMI undergoing PCI.

People with UA/NSTEMI with PCI

In UA/NSTEMI, ticagrelor was cost effective in scenario 1, with low uncertainty within that scenario. Prasugrel was the most cost-effective option in scenarios 2 and 3, with it being the most cost effective option in 60% and 98% of simulations respectively. The committee agreed that although ISAR-REACT 5 demonstrated prasugrel was the most effective antiplatelet, there was some level of uncertainty regarding its applicability to UK practice, as people recruited to the trial underwent PCI within hours, whereas in the NHS time to angiography is can be up to 3 days or longer. As there was some degree of uncertainty regarding how much weight could be placed on the scenarios which utilise the ISAR-REACT 5 data, the committee agreed it was reasonable to make a recommendation to use either prasugrel or ticagrelor in this population.

People not undergoing PCI

One published cost effectiveness analysis looking at medically managed people showed that ticagrelor was cost effective compared to clopidogrel with an ICER of £2,925 per QALY

gained. Given this and the clinical evidence the committee made a recommendation to offer ticagrelor for those who are medically managed, unless they have a high bleeding risk. As discussed in the benefit and harm section above the committee noted that clinical studies often exclude older people or people with a higher risk of bleeding and they were concerned about whether the benefit harm trade off would be the same in this population. Given this the available cost effectiveness evidence may not be generalizable to this population.

1.8.3 Other factors the committee took into account

It was noted that the Summary of Product Characteristics for Prasugrel includes a specific warning that the agent should only be given to those aged 75 and over after a careful individual risk assessment. This derives from the Triton study in which adverse effects, particularly from bleeding, were commoner in this age group (and in people weighing <60Kg). In later studies a reduced dose of prasugrel was used, and an excess bleeding risk in comparison to either clopidogrel or ticagrelor was not seen, but these studies were smaller than Triton with fewer subjects aged ≥75. Across the various studies evidence of benefit from prasugrel in older subjects was also less clearcut than in the overall population, but this is partly due to smaller numbers of subjects and partly because the age-specific data is not always apparent. The committee agreed tp include reference to the need for dose reduction within its recommendations for prasugrel, and a research recommendation was produced with the aim of comparing prasugrel, ticagrelor and clopidogrel in people with ACS aged 75 and over.

The committee was aware that recommending prasugrel for people with STEMI undergoing PCI would be a significant change in practice, as a majority of people are currently given ticagrelor or clopidogrel. Audit data from the British Cardiovascular Intervention Society showed that in 2017-18 47.5% of people with STEMI that underwent PCI received ticagrelor and 7.2% were on prasugrel. It can be assumed the rest of people were taking clopidogrel. For those currently using clopidogrel there will be an increase in costs and for those currently using ticagrelor there will be a decrease. The committee agreed that as the use of ticagrelor and clopidogrel is similar, there will be some savings from people switching from ticagrelor to prasugrel, but there will be more spending for those switching from clopidogrel and prasugrel, due to the larger difference in costs between these two drugs. As a result there will be a resource impact to the NHS in England overall. Audit data for UA/NSTEMI showed that 40.2% of people that underwent PCI were on ticagrelor and 1% were on prasugrel. It can be assumed the rest of people were taking clopidogrel. As a recommendation for both prasugrel and ticagrelor was made, this will lead to a substantial resource impact as both interventions cost more than clopidogrel. The number of people that are medically managed has been decreasing and audit data reported by MINAP showed that in 2017-18 84.6% of people with NSTEMI underwent an angiogram. Of these people, 82.57% underwent PCI. Audit data were not available on the use of dual-antiplatelet therapy for the UA/NSTEMI population that are medically managed, but it is likely to be similar to the PCI population as people currently tend to use the same DAPT for all ACS. As a result, the committee agreed there may be a resource impact of recommending ticagrelor in this group.

Whilst observational data has not been included in this review, the committee felt that it was important to note published UK registry data that aimed to assess mortality associated with ticagrelor, prasgurel and clopidogrel. The registry data showed that prasugrel is associated with fewer mortality events than ticagrelor and clopidogrel.[173] This is consistent with the findings from the ISAR-REACT 5 trial.

When reviewing the evidence for DAPT, the committee noticed that there were existing recommendations for the early administration of aspirin to people with acute UA/NSTEMI, and management advice for people with aspirin sensitivity, in CG94 which apply equally to people with STEMI. They agreed that the updated guideline should be adjusted so that the recommendations cover both STEMI and UA/NSTEMI. As part of the same discussion,

committee members commented that they had seen instances of DAPT being given before confirmation that pain was due to cardiac ischaemia, for example to people with pain from peptic ulceration. This could have significant adverse consequences and a consensus recommendation was therefore agreed advising against administering two anti-platelet agents before ACS has been confirmed as the cause of symptoms.

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Appendices

Appendix A: Review protocols

Table 21: Review protocol: Which antiplatelet is most clinically and cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults?

ID	Field	Content
0.	PROSPERO registration number	CRD42019147580
1.	Review title	Which antiplatelet is most clinically and cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults?
2.	Review question	Which antiplatelet is most clinically and cost effective for managing unstable angina or NSTEMI or for managing STEMI in adults?
3.	Objective	To determine the most clinically effective antiplatelet therapy in patients with UA/NSTEMI and those with STEMI Rationale for including this question: Current NICE technology appraisal guidance recommends prasugrel (in PCI only) and ticagrelor (in combination with aspirin) as options for people with ACS. This guidance will be incorporated unchanged to this guideline. However, there is the outstanding clinical issue about which of the available options (of clopidogrel, prasugrel and ticagrelor) should be the first choice. This review aims to provide guidance on this. Evidence is emerging on newer anti-platelets such as prasugrel.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL)

		• Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Cinahl Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.
5.	Condition or domain being studied	Acute coronary syndrome
6.	Population	Inclusion: People with acute coronary syndromes (UA/NSTEMI and STEMI) Analysed as the overall ACS population, STEMI + revascularisation, UA/NSTEMI + revascularisation and UA/NSTEMI with no revascularisation No stratification – population and management strategy subgroups will be investigated irrespective of heterogeneity

		Exclusion: None
7.	Intervention/Exposure/Test	The following drug combinations will be included: • Clopidogrel + aspirin • Prasugrel + aspirin • Ticagrelor + aspirin Must be initiated as part of acute management: for example peri-procedural, or during index hospitalisation.
8.	Comparator/Reference standard/Confounding factors	• Pairwise comparisons of the above dual antiplatelet therapies
9.	Types of study to be included	• Randomised Controlled Trials (RCT) • Systematic Reviews (SR) of RCTs Non-randomised studies will be excluded.
10.	Other exclusion criteria	• If management in post-acute period • If study population selected for high platelet reactivity (HPR)/ high on-treatment platelet reactivity (HTPR) while on clopidogrel • Non-English language studies • Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	• All-cause mortality – up to 30 days • All-cause mortality at 1 year • Cardiac mortality – up to 30 days • Cardiac mortality at 1 year • Re-infarction up to 30 days • Re- infarction at 1 year

		• Complications related to bleeding including haemorrhagic stroke the following hierarchy of bleeding scales will be used:
		  ○ BARC
		  ○ Author's definition
		  ○ TIMI
		  ○ GUSTO
		
		• Where possible, bleeding outcomes will be categorised into:
		  ○ Major bleeding (including BARC 3-5, TIMI, GUSTO and as reported by author)
		  ○ Minor bleeding (including BARC 1-2, TIMI, GUSTO and as reported by author)
		
		• Health-related quality of life including EQ5D and SF-36.

13.	Secondary outcomes (important outcomes)	• Stroke (any, type not specified) • Need for revascularisation • Early and late, probably or definite stent thrombosis • Breathing adverse effects • Bradycardic adverse effects (bradycardia, pauses and pacemaker insertion) • Other adverse effects of treatment • Unplanned urgent readmission within 30 days for any reason Where multiple time points are reported up to and including 30 days, only 30 day outcomes will be included. Where multiple time points beyond 30 days are reported and including up to 1 year, only up to 1 year outcomes will be reported.

		Where 30-day outcomes are not reported, we will include the next longest follow-up; where up to 1 year outcomes are not reported
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

		• Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.

17.	Analysis of sub-groups	• Timing of pre- and post-hospital admission administration of study drug		
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	19/06/18		
22.	Anticipated completion date	14/05/20		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑

		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
24.	Named contact	**5a. Named contact** National Guideline Centre **5b Named contact e-mail** Acutecoronarysyndromes@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: • Dr Bernard Higgins [Guideline lead] • Dr Saoussen Ftouh/Ms Sedina Lewis/Ms Katherine Jones [Senior Systematic Reviewers; Systematic Reviewer] • Ms Annabelle Davies/Ms Kate Lovibond [Health economist; Health economists lead] • Ms Agnes Cuyas/Ms Jill Cobb [Information specialists]		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be		

		documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Acute coronary syndrome, anti-platelets, NSTEMI, unstable angina, STEMI
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☐ Ongoing ☒ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

Table 22: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2003 that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[123] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in

	discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 (including any such studies included in the previous guidelines) will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. • The following will be rated as 'Very serious limitations' and excluded: economic analyses undertaken as part of clinical studies that are excluded from the clinical review; economic models where relative treatment effects are based entirely on studies that are excluded from the clinical review.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[123]

For more information, please see the Methods report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 23: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 16 June 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 16 June 2019	Exclusions Randomised controlled trials
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 6 of 12 CENTRAL to 2019 Issue 6 of 12	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16

18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	(clopidogrel or plavix or grepid).ti,ab.
39.	(ticagrelor or brilinta or brilique or possia).ti,ab.
40.	Prasugrel Hydrochloride/
41.	(prasugrel or efient or effient or prasita).ti,ab.
42.	p2y12 inhibitors.ti,ab.
43.	*Platelet Aggregation Inhibitors/
44.	(antiplatelet* adj2 (dual or therap* or treat* or combi*)).ti,ab.
45.	DAPT.ti,ab.
46.	or/38-45
47.	37 and 46
48.	randomized controlled trial.pt.
49.	controlled clinical trial.pt.
50.	randomi#ed.ti,ab.
51.	placebo.ab.
52.	randomly.ti,ab.
53.	Clinical Trials as topic.sh.
54.	trial.ti.
55.	or/48-54
56.	Meta-Analysis/
57.	exp Meta-Analysis as Topic/
58.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
59.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
60.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

61.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
62.	(search* adj4 literature).ab.
63.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
64.	cochrane.jw.
65.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
66.	or/56-65
67.	47 and (55 or 66)
68.	ASPIRIN/
69.	(aspirin or caprin or disprin or aspro or acetylsalicylic acid or 2-acetoxybenzoic acid or acetylsalicylate or solprin).ti,ab.
70.	or/68-69
71.	Factor Xa Inhibitors/
72.	(factor Xa inhibitors or apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or dabigatran or pradaxa or warfarin or coumadin).ti,ab.
73.	rivaroxaban/
74.	DABIGATRAN/
75.	warfarin/
76.	or/71-75
77.	70 and 76
78.	37 and 77 and (55 or 66)
79.	67 or 78

Embase (Ovid) search terms

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/

22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	(clopidogrel or plavix or grepid).ti,ab.
37.	clopidogrel/
38.	(ticagrelor or brilinta or brilique or possia).ti,ab.
39.	ticagrelor/
40.	(prasugrel or efient or effient or prasita).ti,ab.
41.	prasugrel/
42.	p2y12 inhibitors.ti,ab.
43.	*antithrombocytic agent/
44.	(antiplatelet* adj2 (dual or therap* or treat* or combi*)).ti,ab.
45.	DAPT.ti,ab.
46.	or/36-45
47.	35 and 46
48.	random*.ti,ab.
49.	factorial*.ti,ab.
50.	(crossover* or cross over*).ti,ab.
51.	((doubl* or singl*) adj blind*).ti,ab.
52.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
53.	crossover procedure/
54.	single blind procedure/
55.	randomized controlled trial/
56.	double blind procedure/
57.	or/48-56
58.	systematic review/
59.	meta-analysis/
60.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
61.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
62.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
63.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
64.	(search* adj4 literature).ab.

65.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
66.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
67.	cochrane.jw.
68.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
69.	or/58-67
70.	47 and (57 or 69)
71.	acetylsalicylic acid/
72.	(aspirin or caprin or disprin or aspro or acetylsalicylic acid or 2-acetoxybenzoic acid or acetylsalicylate or solprin).ti,ab.
73.	71 or 72
74.	blood clotting factor 10a inhibitor/
75.	(factor Xa inhibitors or apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or dabigatran or pradaxa or warfarin or coumadin).ti,ab.
76.	apixaban/
77.	rivaroxaban/
78.	edoxaban/
79.	dabigatran/
80.	warfarin/
81.	or/74-80
82.	73 and 81
83.	35 and 82 and (57 or 69)
84.	70 or 83

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Acute Coronary Syndrome] this term only
#2.	MeSH descriptor: [Angina Pectoris] this term only
#3.	MeSH descriptor: [Angina, Unstable] this term only
#4.	MeSH descriptor: [Coronary Thrombosis] this term only
#5.	MeSH descriptor: [Myocardial Infarction] explode all trees
#6.	(or #1-#5)
#7.	MeSH descriptor: [Heart Arrest] this term only
#8.	(acute coronary near/2 syndrome*):ti,ab
#9.	((myocardial or heart) next infarct*):ti,ab
#10.	(heart next (attack* or event*)):ti,ab
#11.	((heart or cardiac) next arrest*):ti,ab
#12.	(coronary near/2 thrombos*):ti,ab
#13.	(stemi or st-segment or st segment or st-elevation or st elevation):ti,ab
#14.	non-ST-segment elevation:ti,ab
#15.	(non-STEMI or NSTEMI or nonSTEMI):ti,ab
#16.	Q wave myocardial infarction:ti,ab
#17.	non Q wave MI:ti,ab
#18.	NSTE-ACS:ti,ab
#19.	(subendocardial near/3 infarct*):ti,ab
#20.	((unstable or variant) near/2 angina*):ti,ab
#21.	(unstable near/2 coronary):ti,ab

#22.	(or #6-#21)
#23.	(clopidogrel or plavix or grepid):ti,ab
#24.	(ticagrelor or brilinta or brilique or possia):ti,ab
#25.	MeSH descriptor: [Prasugrel Hydrochloride] this term only
#26.	(prasugrel or efient or effient or prasita):ti,ab
#27.	p2y12 inhibitors:ti,ab
#28.	MeSH descriptor: [Platelet Aggregation Inhibitors] this term only
#29.	(antiplatelet* near/2 (dual or therap* or treat* or combi*)):ti,ab
#30.	DAPT:ti,ab
#31.	(or #23-#30)
#32.	#22 and #31
#33.	MeSH descriptor: [Aspirin] this term only
#34.	(aspirin or caprin or disprin or aspro or acetylsalicylic acid or 2-acetoxybenzoic acid or acetylsalicylate or solprin):ti,ab
#35.	(or #33-#34)
#36.	MeSH descriptor: [Factor Xa Inhibitors] this term only
#37.	(factor Xa inhibitors or apixaban or eliquis or rivaroxaban or xarelto or edoxaban or lixiana or dabigatran or pradaxa or warfarin or coumadin):ti,ab
#38.	MeSH descriptor: [Rivaroxaban] this term only
#39.	MeSH descriptor: [Dabigatran] this term only
#40.	MeSH descriptor: [Warfarin] this term only
#41.	(or #36-#40)
#42.	#35 and #41
#43.	#32 or #42

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a search relating to acute coronary syndromes population combined with terms for interventions in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase using a filter for health economics studies.

Table 24: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Embase	01 January 2014 – 18 June 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - 2003 – 31 March 2018 NHSEED - 2003 to 31 March 2015	None

Medline (Ovid) search terms

1.	Acute Coronary Syndrome/ or Angina Pectoris/ or Angina, Unstable/ or Coronary Thrombosis/ or exp Myocardial Infarction/
2.	Heart Arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.
7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter/
19.	editorial/
20.	news/
21.	exp historical article/
22.	Anecdotes as Topic/
23.	comment/
24.	case report/
25.	(letter or comment*).ti.
26.	or/18-25
27.	randomized controlled trial/ or random*.ti,ab.
28.	26 not 27
29.	animals/ not humans/
30.	exp Animals, Laboratory/
31.	exp Animal Experimentation/
32.	exp Models, Animal/
33.	exp Rodentia/
34.	(rat or rats or mouse or mice).ti.
35.	or/28-34
36.	17 not 35
37.	limit 36 to English language
38.	Economics/
39.	Value of life/

40.	exp "Costs and Cost Analysis"/
41.	exp Economics, Hospital/
42.	exp Economics, Medical/
43.	Economics, Nursing/
44.	Economics, Pharmaceutical/
45.	exp "Fees and Charges"/
46.	exp Budgets/
47.	budget*.ti,ab.
48.	cost*.ti.
49.	(economic* or pharmaco?economic*).ti.
50.	(price* or pricing*).ti,ab.
51.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
52.	(financ* or fee or fees).ti,ab.
53.	(value adj2 (money or monetary)).ti,ab.
54.	or/38-53
55.	37 and 54
56.	*Angiography/
57.	Angiocardiography/
58.	Coronary Angiography/
59.	Angiograph*.ti.
60.	Arteriograph*.ti.
61.	Angiocardiograph*.ti,ab.
62.	Coronary Angiograph*.ti,ab.
63.	Angiogram*.ti,ab.
64.	Cardioangiograph*.ti,ab.
65.	Angiocardiogram.ti,ab.
66.	Angio Cardiograph*.ti,ab.
67.	Coronary Arteriogra*.ti,ab.
68.	Coronarograph*.ti,ab.
69.	*Myocardial Revascularization/
70.	Angioplasty, Balloon, Coronary/
71.	(Myocardial adj revasculari?ation).ti,ab.
72.	PCI.ti,ab.
73.	Percutaneous coronary intervention.ti,ab.
74.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
75.	PTCA.ti,ab.
76.	exp Angioplasty/
77.	Blunt microdissection.ti,ab.
78.	((laser or patch) adj angioplasty).ti,ab.
79.	Percutaneous Transluminal Angioplasty.ti,ab.
80.	Transluminal Coronary Angioplasty.ti,ab.
81.	(Balloon adj3 coronary).ti,ab.
82.	(Balloon adj3 angioplasty).ti,ab.

83.	exp STENTS/
84.	stent*.ti,ab.
85.	Or/56-84
86.	aspirin/
87.	(aspirin or acetylsalicylic acid).ti,ab.
88.	(clopidogrel or plavix).ti,ab.
89.	(ticagrelor or brilique).ti,ab.
90.	(prasugrel or efient or effient or prasita).ti,ab.
91.	Prasugrel Hydrochloride/
92.	platelet aggregation inhibitors/
93.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
94.	exp Platelet Glycoprotein GPIIb-IIIa Complex/
95.	exp Receptors, Fibrinogen/
96.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
97.	exp adrenergic beta-antagonists/
98.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
99.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or celiprolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/
100.	(beta adj3 block*).ti,ab.
101.	(b adj3 block*).ti,ab.
102.	(beta adj2 antagonist*).ti,ab.
103.	Antithrombins/
104.	Antithrombin*.ti,ab.
105.	(thrombin adj3 inhibitor*).ti,ab.
106.	Hirudins/
107.	Hirudin*.ti,ab.
108.	Hirulog.ti,ab.
109.	Bivalirudin.ti,ab.
110.	Or/86-109
111.	55 and (85 or 110)

Embase (Ovid) search terms

1.	acute coronary syndrome/ or angina pectoris/ or unstable angina pectoris/ or coronary artery thrombosis/ or exp heart infarction/
2.	heart arrest/
3.	(acute coronary adj2 syndrome*).ti,ab.
4.	((myocardial or heart) adj infarct*).ti,ab.
5.	(heart adj (attack* or event*)).ti,ab.
6.	((heart or cardiac) adj arrest*).ti,ab.

7.	(coronary adj2 thrombos*).ti,ab.
8.	(stemi or st-segment or st segment or st-elevation or st elevation).ti,ab.
9.	"non-ST-segment elevation".ti,ab.
10.	(non-STEMI or NSTEMI or nonSTEMI).ti,ab.
11.	"Q wave myocardial infarction".ti,ab.
12.	"non Q wave MI".ti,ab.
13.	NSTE-ACS.ti,ab.
14.	(subendocardial adj3 infarct*).ti,ab.
15.	((unstable or variant) adj2 angina*).ti,ab.
16.	(unstable adj2 coronary).ti,ab.
17.	or/1-16
18.	letter.pt. or letter/
19.	note.pt.
20.	editorial.pt.
21.	Case report/ or Case study/
22.	(letter or comment*).ti.
23.	or/18-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animal/ not human/
27.	Nonhuman/
28.	exp Animal Experiment/
29.	exp Experimental animal/
30.	Animal model/
31.	exp Rodent/
32.	(rat or rats or mouse or mice).ti.
33.	or/25-32
34.	17 not 33
35.	limit 34 to English language
36.	health economics/
37.	exp economic evaluation/
38.	exp health care cost/
39.	exp fee/
40.	budget/
41.	funding/
42.	budget*.ti,ab.
43.	cost*.ti.
44.	(economic* or pharmaco?economic*).ti.
45.	(price* or pricing*).ti,ab.

46.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
47.	(financ* or fee or fees).ti,ab.
48.	(value adj2 (money or monetary)).ti,ab.
49.	or/36-48
50.	35 and 49
51.	angiography/
52.	angiocardiography/
53.	coronary angiography/
54.	Angiograph*.ti.
55.	Arteriograph*.ti.
56.	Angiocardiograph*.ti,ab.
57.	Coronary Angiograph*.ti,ab.
58.	Angiogram*.ti,ab.
59.	Cardioangiograph*.ti,ab.
60.	Angiocardiogram.ti,ab.
61.	Angio Cardiograph*.ti,ab.
62.	Coronary Arteriogra*.ti,ab.
63.	Coronarograph*.ti,ab.
64.	*heart muscle revascularization/
65.	transluminal coronary angioplasty/
66.	(Myocardial adj revasculari?ation).ti,ab.
67.	PCI.ti,ab.
68.	Percutaneous coronary intervention.ti,ab.
69.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
70.	PTCA.ti,ab.
71.	*angioplasty/
72.	Blunt microdissection.ti,ab.
73.	((laser or patch) adj angioplasty).ti,ab.
74.	Percutaneous Transluminal Angioplasty.ti,ab.
75.	Transluminal Coronary Angioplasty.ti,ab.
76.	(Balloon adj3 coronary).ti,ab.
77.	(Balloon adj3 angioplasty).ti,ab.
78.	exp STENTS/
79.	stent*.ti,ab.
80.	Or/51-79
81.	acetylsalicylic acid/
82.	(aspirin or acetylsalicylic acid).ti,ab.
83.	(clopidogrel or plavix).ti,ab.
84.	(ticagrelor or brilique).ti,ab.

85.	(prasugrel or efient or effient or prasita).ti,ab.
86.	prasugrel/
87.	antithrombocytic agent/
88.	(Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA).ti,ab.
89.	exp fibrinogen receptor/
90.	(Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat).ti,ab.
91.	abciximab/ or eptifibatide/ or tirofiban/
92.	exp beta adrenergic receptor blocking agent/
93.	(propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim).ti,ab.
94.	propranolol/ or acebutolol/ or atenolol/ or bisoprolol/ or bisoprolol fumarate/ or carvedilol/ or celiprolol/ or esmolol/ or labetalol/ or metoprolol/ or nadolol/ or nebivolol/ or oxprenolol/ or pindolol/ or sotalol/ or timolol/ or timolol maleate/
95.	(beta adj3 block*).ti,ab.
96.	(b adj3 block*).ti,ab.
97.	(beta adj2 antagonist*).ti,ab.
98.	antithrombin/
99.	Antithrombin*.ti,ab.
100.	(thrombin adj3 inhibitor*).ti,ab.
101.	hirudin derivative/
102.	Hirudin*.ti,ab.
103.	Hirulog.ti,ab.
104.	Bivalirudin.ti,ab.
105.	Or/81-104
106.	50 and (80 or 105)

NHS EED and HTA (CRD) search terms

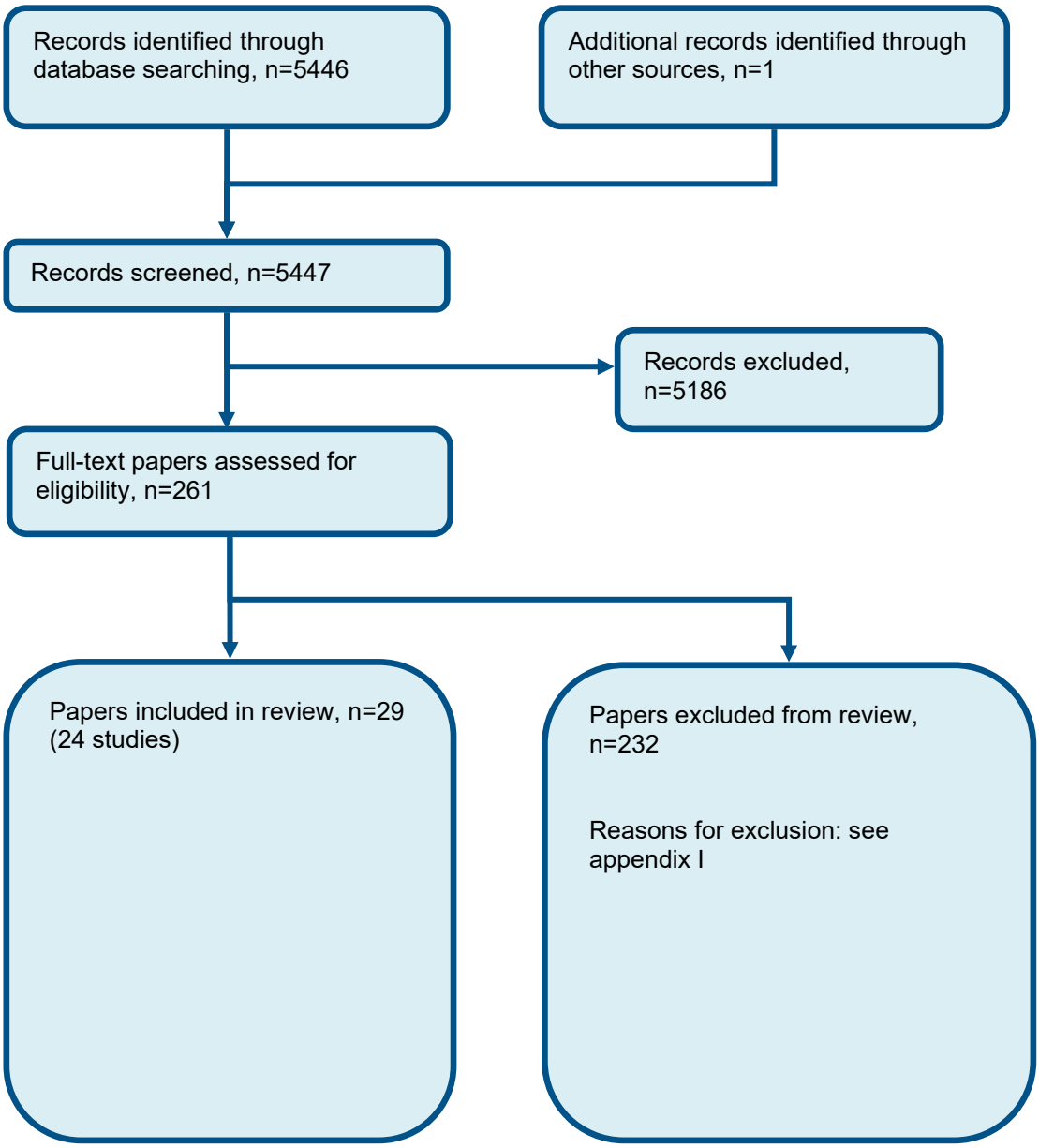
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute coronary adj2 syndrome*))
#9.	(((myocardial or heart) adj infarct*))
#10.	((heart adj (attack* or event*)))
#11.	(((heart or cardiac) adj arrest*))
#12.	((coronary adj2 thrombos*))

#13.	((stemi or st-segment or st segment or st-elevation or st elevation))
#14.	("non-ST-segment elevation")
#15.	((non-STEMI or NSTEMI or nonSTEMI))
#16.	("Q wave myocardial infarction")
#17.	("non Q wave MI")
#18.	(NSTE-ACS)
#19.	(STE-ACS)
#20.	(((subendocardial adj3 infarct*)))
#21.	((((unstable or variant) adj2 angina*)))
#22.	(((unstable adj2 coronary)))
#23.	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24.	(MeSH DESCRIPTOR Angiography)
#25.	(MeSH DESCRIPTOR Angiocardiography)
#26.	((MeSH DESCRIPTOR Coronary Angiography))
#27.	((Angiograph*))
#28.	((Arteriograph*))
#29.	((Angiocardiograph*))
#30.	((Coronary Angiograph*))
#31.	((Angiogram*))
#32.	((Cardioangiograph*))
#33.	((Angiocardiogram))
#34.	((Angio Cardiograph*))
#35.	((Coronary Arteriogra*))
#36.	((Coronarograph*))
#37.	(MeSH DESCRIPTOR Myocardial Revascularization)
#38.	(MeSH DESCRIPTOR Angioplasty, Balloon, Coronary)
#39.	(((Myocardial adj revasculari?ation)))
#40.	((PCI))
#41.	((Percutaneous coronary intervention))
#42.	((Percutaneous Transluminal Coronary Angioplasty))
#43.	((PTCA))
#44.	(MeSH DESCRIPTOR Angioplasty EXPLODE ALL TREES)
#45.	((Blunt microdissection))
#46.	((((laser or patch) adj angioplasty)))
#47.	((Percutaneous Transluminal Angioplasty))
#48.	((Transluminal Coronary Angioplasty))
#49.	(((Balloon adj3 coronary)))
#50.	((Balloon adj3 angioplasty))
#51.	(MeSH DESCRIPTOR Stents EXPLODE ALL TREES)
#52.	((stent*))
#53.	(#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
#54.	(MeSH DESCRIPTOR Aspirin)

#55.	((aspirin or acetylsalicylic acid))
#56.	((clopidogrel or plavix))
#57.	((ticagrelor or brilique))
#58.	((prasugrel or efient or effient or prasita))
#59.	MeSH DESCRIPTOR Prasugrel Hydrochloride
#60.	MeSH DESCRIPTOR Platelet Aggregation Inhibitors
#61.	((Glycoproteins IIb-IIIa or GPIIb-IIIa Receptors or Integrin alpha-IIb beta-3 or Integrin alphaIIbbeta3 or GPIIB IIIA))
#62.	MeSH DESCRIPTOR Platelet Glycoprotein GPIIb-IIIa Complex EXPLODE ALL TREES
#63.	MeSH DESCRIPTOR Receptors, Fibrinogen EXPLODE ALL TREES
#64.	((Abciximab or Reopro or Eptifibatide or Integrelin or Integrilin or Intrifiban or Tirofiban or Aggrastat))
#65.	MeSH DESCRIPTOR Adrenergic beta-Antagonists EXPLODE ALL TREES
#66.	((propranolol or angilol or inderal-la or half-inderal or inderal or bedranol or prograne or slo-pro or acebutolol or sectral or atenolol or tenormin or bisoprolol or cardicor or emcor or carvedilol or eucardic or celiprolol or celectol or co-tenidone or tenoret or tenoretic or esmolol or brevibloc or labetalol or trandate or metoprolol or betaloc or lopresor or nadolol or corgard or nebivolol or nebilet or hypoloc or oxprenolol or trasicor or slow-trasicor or pindolol or visken or sotalol or beta-cardone or sotacor or timolol or betim))
#67.	(MeSH DESCRIPTOR propranolol)
#68.	(MeSH DESCRIPTOR acebutolol)
#69.	(MeSH DESCRIPTOR atenolol)
#70.	(MeSH DESCRIPTOR bisoprolol)
#71.	(MeSH DESCRIPTOR celiprolol)
#72.	(MeSH DESCRIPTOR labetalol)
#73.	(MeSH DESCRIPTOR metoprolol)
#74.	(MeSH DESCRIPTOR nadolol)
#75.	(MeSH DESCRIPTOR nebivolol)
#76.	(MeSH DESCRIPTOR oxprenolol)
#77.	(MeSH DESCRIPTOR pindolol)
#78.	(MeSH DESCRIPTOR sotalol)
#79.	(MeSH DESCRIPTOR timolol)
#80.	((beta adj3 block*))
#81.	((b adj3 block*))
#82.	((beta adj2 antagonist*))
#83.	MeSH DESCRIPTOR Antithrombins
#84.	(Antithrombin*)
#85.	((thrombin adj3 inhibitor*))
#86.	MeSH DESCRIPTOR Hirudins
#87.	(Hirudin*)
#88.	(Hirulog)
#89.	(Bivalirudin)
#90.	#54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89
#91.	(#23 AND (#53 OR #90))

Appendix C: Clinical evidence selection

Figure 4: Flow chart of clinical study selection for the review of antiplatelet therapy



Appendix D: Clinical evidence tables

Study	Alexopoulos 2012[8]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=55)
Countries and setting	Conducted in Greece; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 5 days follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	STEMI: Undergoing primary percutaneous coronary intervention with stent implantation.
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Patients were excluded if they had a history of stroke/transient ischaemic attack, bleeding diathesis, chronic oral anticoagulation treatment, previous antiplatelet treatment, contraindications to antiplatelet therapy, PCI or coronary artery bypass grafting <3 months, haemodynamic instability, platelet count <100,000/μL, haematocrit <30%, creatinine clearance <30 mL/min, severe hepatic dysfunction, use of strong CYP3A inhibitors or inducers, increased risk of bradycardia, severe chronic obstructive pulmonary disease, or periprocedural IIb/IIIa inhibitors administration
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 58 (12 years); prasugrel group: 61 (13 years). Gender (M:F): 44/11. Ethnicity: Not reported
Further population details	
Extra comments	'STEMI patients undergoing primary PCI with stent implantation'. Patient's randomisation followed by immediate administration of the study drug was performed in the catheterisation laboratory, directly after angiography
Indirectness of population	No indirectness
Interventions	(n=28) Intervention 1: Antiplatelet - Ticagrelor. 180mg loading dose followed by 90mg bid maintenance dose starting 12±6 hours post loading dose, until day 5. All patients received oral aspirin 325mg at first medical contact. After PCI, all patients received aspirin 100mg/d indefinitely. Duration 5 days. Concurrent medication/care: All patients received 70 U/kg of unfractionated heparin intravenously at first medical contact

Study	Alexopoulos 2012[8]
	and additional heparin or bivalirudin at the time of PCI per operator's discretion . Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=27) Intervention 2: Antiplatelet - Prasugrel. Prasugrel 60mg loading dose followed by 10mg daily maintenance dose starting 24 hours post loading dose, until day 5. All patients received oral aspirin 325mg at first medical contact. After PCI, all patients received aspirin 100mg/d indefinitely. Duration 5 days. Concurrent medication/care: All patients received 70 U/kg of unfractionated heparin intravenously at first medical contact and additional heparin or bivalirudin at the time of PCI per operator's discretion . Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable
Funding	Academic or government funding (Study supported by the Research Committee of the Patras University Medical School)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus PRASUGREL

Protocol outcome 1: All-cause mortality at up to 30 days
- Actual outcome for STEMI: All-cause mortality (death) at 5 days; Group 1: 1/28, Group 2: 3/27
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There were no differences in demographic and clinical characteristics between the 2 groups'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Complications related to bleeding (including haemorragic stroke) at Define
- Actual outcome for STEMI: Complications related to bleeding (major) at 5 days; Group 1: 0/28, Group 2: 0/27
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There were no differences in demographic and clinical characteristics between the 2 groups'; Blinding details: 'single-blind study...Physicians and operators who performed platelet function testing were blind to the actual drug used, whereas an independent physician monitored bleeding and adverse event data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Complications related to bleeding (minor or minimal) at 5 days; Group 1: 3/28, Group 2: 1/27
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'There were no differences in demographic and clinical characteristics between the 2 groups'; Blinding details: 'single-blind study...Physicians and operators who performed platelet function testing were blind to the actual drug used, whereas an independent physician monitored bleeding and adverse event data'; Group 1 Number missing: ; Group 2 Number missing:

Study	Alexopoulos 2012[8]
Protocol outcomes not reported by the study	Quality of life; Cardiac mortality at 30 days ; Stroke; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	Angiolillo 2016[12]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in USA; Setting: 15 US centres
Line of therapy	Unclear
Duration of study	Intervention + follow up: Pharmacodynamic outcomes reported at end of percutaneous coronary intervention
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnostic angiography. NSTE-ACS was defined as the presence of cardiac ischaemic symptoms with ischaemic changes (but not ST segment elevation) on electrocardiogram. However, normal electrocardiograms could be acceptable if the investigator considered an ACS presentation likely
Stratum	Overall: Low-risk ACS undergoing ad-hoc PCI
Subgroup analysis within study	Not applicable
Inclusion criteria	From online appendix: provision of informed consent prior to any study-specific procedures; female and/or male aged 18 years or older; patients with documented ACS who were troponin negative and undergoing ad-hoc PCI ("ad hoc PCI" is when PCI was performed immediately following diagnostic angiography); women must have been post-menopausal or surgically sterile with a negative urine pregnancy test. Women over 50 years of age were considered post-menopausal if they had been amenorrhoeic for 12 months without an alternative medical cause following cessation of all exogenous hormonal treatment; patients on aspirin as an antiplatelet medication
Exclusion criteria	From online appendix: contraindication or other reason that clopidogrel or ticagrelor should not have been administered (e.g. hypersensitivity, active bleeding, severe liver disease, history of previous intracranial bleed, gastrointestinal bleed within the past 6 months, major surgery within 30 days; use of any thienopyridine or ticagrelor within 7 days prior to randomisation; any indication for chronic oral anticoagulation (e.g. atrial fibrillation, mitral stenosis, or prosthetic heart valve); concomitant therapy with

Study	Angiolillo 2016[12]
	strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir), CYP3A substrates with narrow therapeutic index (e.g. cyclosporine, quinidine), or strong CYP3A inducers (e.g. rifampin/rifampicin, phenytoin, carbamazepine); increased bleeding risk, including: recent (within 30 days) GI bleeding; any history of intracranial, intraocular, retroperitonal, or spinal bleeding; recent (within 30 days of dosing) major trauma; sustained uncontrolled hypertension (systolic blood pressure >180mmHg or diastolic blood pressure >100mmHg; history of haemorrhagic disorders that can increase the risk of bleeding (e.g. haemophilia, von Willebrand's disease); inability to discontinue concomitant therapy with non-selective non-steroidal anti-inflammatory drug at screening; platelet count <100,000 or haemoglobin <10g/dL; known hepatic disease or any liver function test >3x upper limit of normal; any history of intolerance or allergy to ASA; patient required dialysis; participation in another investigational drug or device study within 30 days of dosing; any acute or chronic unstable condition in the past 30 days or other condition that, in the opinion of the investigator, may have either put the patient at risk or influenced the result of the study (e.g. active cancer, risk for non-compliance, risk for being lost to follow-up); patients who had been treated with glycoprotein IIb/IIIa inhibitor drugs, 14 days before randomisation for abciximab, and up to 24 hours before randomisation for eptifibatide and tirofiban, or at any time during the study; involvement in the planning and conduct of the study (applied to AstraZeneca or delegate staff, and study site staff); previous enrollment or randomisation of treatment in the present study; a suspected/manifest infection according to the World Health Organization risk categories 2, 3, and 4
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 60.1 (10.7); clopidogrel group: 63.0 (9.1). Gender (M:F): 70/30. Ethnicity: Ticagrelor group: 71.7% white, 23.9% black or African American, 4.4% other; clopidogrel group: 71.7% white; 23.9% black or African American; 4.3% other
Further population details	
Extra comments	Any use of the following medication s was prohibited during the study:treatment with approved oral anticoagulants was not allowed 10 days prior to randomisation and during the study (to make sure that warfarin or other oral anticoagulants were not given in combination with ticagrelor); patients taking>3 doses of NSAIDs within 10 days prior to randomisation. No NSAIDs were allowed during the study; After diagnostic angiography, troponin-negative ACS patients undergoing ad hoc PCI were randomly assigned (1:1) to treatment groups
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Antiplatelet - Ticagrelor. 180mg loading dose of ticagrelor after diagnostic angiography, then 90mg maintenance dose 12±1 hour after the loading dose. Study drug loading dose was administered in the catheterisation laboratory after defining coronary anatomy and before starting PCI.

Study	Angiolillo 2016[12]
	Afterwards, antiplatelet treatment was left to the discretion of the treating physician. All patients received a loading dose of aspirin, as per institutional standards (160-500mg), and then 75 to 100mg daily. Duration Unclear. Concurrent medication/care: Morphine use in catheterisation laboratory. Access site, choice of anticoagulant, stent type and procedural technique were at the physicians's discretion. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=49) Intervention 2: Antiplatelet - Clopidogrel. 600mg loading dose of clopidogrel after diagnostic angiography. Study drug loading dose was administered in the catheterisation laboratory after defining coronary anatomy and before starting PCI. Afterwards, antiplatelet treatment was left to the discretion of the treating physician. All patients received a loading dose of aspirin (160-500mg), as per institutional standards, and then 75 to 100mg daily. Duration Unclear. Concurrent medication/care: Morphine use in catheterisation laboratory. Access site, choice of anticoagulant, stent type and procedural technique were at the physicians's discretion. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable
Funding	Study funded by industry (This study was supported by AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for UA/NSTEMI: All-cause mortality (death) at 30 days; Group 1: 0/51, Group 2: 0/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar...with the exception of prior coronary artery bypass graft', which had more cases in the clopidogrel group (p=0.0168). More people in the clopidogrel group also had hypertension (p=0.0599) and prior myocardial infarction (p=0.0832); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Other adverse effects of treatment at Define

- Actual outcome for UA/NSTEMI: Other adverse effects (any adverse event) at 30 days; Group 1: 15/51, Group 2: 9/49
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar...with the exception of prior coronary artery bypass graft', which had more cases in the clopidogrel group (p=0.0168). More people in the clopidogrel group also had hypertension (p=0.0599) and prior myocardial infarction (p=0.0832); Blinding details: 'Members of the clinical staff who managed patient care were blinded to the study drug throughout the PCI procedure until final assessment of bleeding, approximately 1 hour after sheath removal. Thereafter, the study became open-label'; Group 1 Number missing: ; Group 2 Number missing:

Study	Angiolillo 2016[12]
Protocol outcome 3: Complications related to bleeding (including haemorragic stroke) - Actual outcome for UA/NSTEMI: Complications related to bleeding (minor) at 30 days; Group 1: 2/51, Group 2: 0/49 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar...with the exception of prior coronary artery bypass graft', which had more cases in the clopidogrel group (p=0.0168). More people in the clopidogrel group also had hypertension (p=0.0599) and prior myocardial infarction (p=0.0832); Blinding details: 'Members of the clinical staff who managed patient care were blinded to the study drug throughout the PCI procedure until final assessment of bleeding, approximately 1 hour after sheath removal. Thereafter, the study became open-label'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Stroke; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Cardiac mortality at 30 days

Study	Bonello 2015[20]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=213)
Countries and setting	Conducted in France; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 1-month follow up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	UA/NSTEMI: Patients with NSTE-ACS and undergoing PCI
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients between 18 and 75 years old who underwent PCI for an intermediate or high-risk NSTE-ACS and agreeing to participate in the study were eligible
Exclusion criteria	Exclusion criteria included ST-elevation ACS, NSTE-ACS medically managed or intended for surgery after PCI, cardiogenic shock, cardiac arrest, contraindication to antiplatelet therapy, treatment with a P2Y12-ADP antagonist <1 month, a platelet count <100 G/L, history of bleeding diathesis, history of haemorrhagic stroke, stroke, recent surgery (<1 month), age ≥75 years old, haemodialysis, weight <60 kg, treatment with a P2Y12-ADP receptor during the previous month, oral anticoagulant therapy, and use of medication with known interference with ticagrelor or prasugrel and bradycardia

Study	Bonello 2015[20]
Recruitment/selection of patients	Consecutive patients with ACS
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 61.5 (10.4 years); prasugrel group: 60 (9.6 years). Gender (M:F): 159/54. Ethnicity: Not reported
Further population details	
Extra comments	Timing of randomisation to treatment unclear
Indirectness of population	No indirectness
Interventions	(n=106) Intervention 1: Antiplatelet - Ticagrelor. Patients received a 180mg loading dose of ticagrelor as soon as possible after diagnosis of NSTE-ACS followed by 90mg twice daily as maintenance dose. All patients received a loading dose of 150mg aspirin IV at the time of PCI. Duration 1 month post-PCI. Concurrent medication/care: All patients received their loading dose at least 4 hours before PCI (13.4 ± 8.3 hours). PCI was performed using the radial route in all cases but 2 patients in the ticagrelor group. All patients received either a bolus of heparin (100 IU/kg) during the procedure followed by ACT-adjusted additional bolus or standard bivalirudin infusion. Drug-eluting stents were used in all patients. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=107) Intervention 2: Antiplatelet - Prasugrel. Patients undergoing PCI received a 60mg loading dose of prasugrel as soon as the coronary anatomy was known and the decision to proceed to PCI taken. They received prasugrel 10mg daily as maintenance dose. All patients received a loading dose of 150mg aspirin IV at the time of PCI. Duration 1 month post-PCI. Concurrent medication/care: All patients received their loading dose at least 4 hours before PCI (13.4 ± 8.3 hours). PCI was performed using the radial route in all cases but 2 patients in the prasugrel group. All patients received either a bolus of heparin (100 IU/kg) during the procedure followed by ACT-adjusted additional bolus or standard bivalirudin infusion. Drug-eluting stents were used in all patients. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (The study was supported by a grant from the Assistance Publique - Hopitaux de Marseille)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus PRASUGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for UA/NSTEMI: All-cause mortality (death) at 30 days; Group 1: 0/106, Group 2: 0/107
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were similar in terms of baseline characteristics'; Group 1 Number missing: ; Group 2 Number missing:

Study	Bonello 2015[20]
	Protocol outcome 2: Cardiac mortality at 30 days - Actual outcome for UA/NSTEMI: Cardiac mortality (cardiovascular death) at 30 days ; Group 1: 0/106, Group 2: 0/107 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were similar in terms of baseline characteristics'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Complications related to bleeding (including haemorragic stroke) - Actual outcome for UA/NSTEMI: Complications related to bleeding (major, BARC >2) at 30 days ; Group 1: 7/106, Group 2: 8/107 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were similar in terms of baseline characteristics'; Blinding details: open-label; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Stroke - Actual outcome for UA/NSTEMI: Stroke (any, type not specified) at 30 days ; Group 1: 0/106, Group 2: 1/107 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were similar in terms of baseline characteristics'; Blinding details: open-label; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	Dasbiswas 2013[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in India; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 weeks treatment (median duration 14.5 weeks) with 90 days follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall: Undergoing percutaneous coronary intervention

Study	Dasbiswas 2013[36]
Subgroup analysis within study	Not applicable
Inclusion criteria	Both male and female patients between 18 and 75 years of age with acute coronary syndrome undergoing PCI. The patients with unstable angina and non-ST-segment elevation MI were enrolled within 72 hours of symptom onset and with ST-segment elevation MI were enrolled either undergoing primary PCI or within 14 days after the onset of symptoms. The patients were required to weigh more than 60kg.
Exclusion criteria	Patients with cardiogenic shock, refractory ventricular arrhythmias, heart failure (NYHA class IV), active bleeding, history of bleeding diatheses, transient ischemic stroke, platelet < 100,000/mm3 and haemoglobin <10 gm% were not eligible to participate in the study.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Prasugrel group, male: 54.8 (9.67); prasugrel group, female: 58.7 (8.10); clopidogrel group, male: 54.6 (9.65); clopidogrel group, female: 60.4 (10.50). Gender (M:F): Not reported. Ethnicity: Not reported
Further population details	
Extra comments	The patient should have adequate liver and kidney function. The patients received a loading dose of the study drug between randomisation and 1 hour after leaving the cardiac catheterisation laboratory
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Antiplatelet - Prasugrel. Loading dose of 60mg prasugrel between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. Following loading dose, patients received prasugrel 10mg once daily. All patients were prescribed aspirin 325mg per day during the study. The maintenance dose was started from the next day of loading dose. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=109) Intervention 2: Antiplatelet - Clopidogrel. Loading dose of 300mg clopidogrel between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. Following loading dose, patients received clopidogrel 75mg once daily. All patients were prescribed aspirin 325mg per day during the study. The maintenance dose was started from the next day of loading dose. Duration 12 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL	

Study	Dasbiswas 2013[36]
	Protocol outcome 1: Other adverse effects of treatment at 30 days - Actual outcome: Other adverse effects (all events) at 30 days; Group 1: 4/111, Group 2: 5/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing - Actual outcome: Other adverse effects (serious adverse event: tonic clonic convulsions with slurred speech and salivation) at 30 days; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: cardiogenic shock) at 30 days; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: acid peptic disease) at 30 days; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: non-cardiac chest pain) at 30 days; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: acute cerebral haemorrhage) at 30 days; Group 1: 1/111, Group 2: 0/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: right groin haematoma) at 30 days; Group 1: 1/111, Group 2: 0/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: right brachial monoparesis) at 30 days; Group 1: 1/111, Group 2: 0/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: reduction in haemoglobin %) at 30 days; Group 1: 1/111, Group 2: 0/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (serious adverse event: other medically important condition - cerebral infarct) at 30 days; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing:

Study	Dasbiswas 2013[36]
Protocol outcome 2: Cardiac mortality at 30 days - Actual outcome: Cardiac mortality at 30 days; Group 1: 0/93, Group 2: 1/96 Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: 18, Reason: At 12 weeks: suspected adverse reactions (n=4); voluntary withdrawal (n=5); medically withdrawn (n=1); death (n=2); PCI not done (n=3); lost to follow-up (n=3); Group 2 Number missing: 13, Reason: At 12 weeks: suspected adverse reactions (n=3); voluntary withdrawal (n=3); death (n=1); PCI not done (n=3); lost to follow-up (n=3) Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke) - Actual outcome: Complications related to bleeding (major bleeding) at 30 days; Group 1: 0/111, Group 2: 0/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (minor bleeding) at 30 days; Group 1: 5/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Stroke - Actual outcome: Stroke (any nonfatal, type not specified) at 30 days; Group 1: 1/93, Group 2: 1/96 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: 18, Reason: At 12 weeks: suspected adverse reactions (n=4); voluntary withdrawal (n=5); medically withdrawn (n=1); death (n=2); PCI not done (n=3); lost to follow-up (n=3); Group 2 Number missing: 13, Reason: At 12 weeks: suspected adverse reactions (n=3); voluntary withdrawal (n=3); death (n=1); PCI not done (n=3); lost to follow-up (n=3) Protocol outcome 5: Need for revascularisation at 30 days - Actual outcome: Need for revascularisation (urgent revascularisation) at 30 days; Group 1: 0/93, Group 2: 0/96 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: 18, Reason: At 12 weeks: suspected adverse reactions (n=4); voluntary withdrawal (n=5); medically withdrawn (n=1); death (n=2); PCI not done (n=3); lost to follow-up (n=3); Group 2 Number missing: 13, Reason: At 12 weeks: suspected adverse reactions (n=3); voluntary withdrawal (n=3); death (n=1); PCI not done (n=3); lost to follow-up (n=3) Protocol outcome 6: Early and late stent thrombosis - Actual outcome: Stent thrombosis (serious adverse event: acute stent thrombosis) at Unclear; Group 1: 0/111, Group 2: 1/109 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: All-cause mortality at 30 days - Actual outcome: All-cause mortality (death) at 30 days; Group 1: 2/111, Group 2: 1/109

Study	Dasbiswas 2013[36]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Re-infarction at 30 days - Actual outcome: Re-infarction (nonfatal myocardial infarction) at 30 days; Group 1: 0/93, Group 2: 0/96 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: 18, Reason: At 12 weeks: suspected adverse reactions (n=4); voluntary withdrawal (n=5); medically withdrawn (n=1); death (n=2); PCI not done (n=3); lost to follow-up (n=3); Group 2 Number missing: 13, Reason: At 12 weeks: suspected adverse reactions (n=3); voluntary withdrawal (n=3); death (n=1); PCI not done (n=3); lost to follow-up (n=3) Protocol outcome 10: Unplanned urgent readmission at within 30 days for any reason - Actual outcome: Unplanned urgent readmission (rehospitalisation due to cardiac event) at 30 days; Group 1: 1/93, Group 2: 1/96 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar age and weight; Group 1 Number missing: 18, Reason: At 12 weeks: suspected adverse reactions (n=4); voluntary withdrawal (n=5); medically withdrawn (n=1); death (n=2); PCI not done (n=3); lost to follow-up (n=3); Group 2 Number missing: 13, Reason: At 12 weeks: suspected adverse reactions (n=3); voluntary withdrawal (n=3); death (n=1); PCI not done (n=3); lost to follow-up (n=3)	
Protocol outcomes not reported by the study	Quality of life; Length of hospital stay

Study	Dehghani 2017[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Canada; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute STEMI on qualifying electrocardiogram (ECG) (≥1mV in ≥2 continuous leads)
Stratum	STEMI: Fibrinolytic-treated patients undergoing early PCI
Subgroup analysis within study	Not applicable:

Study	Dehghani 2017[44]
Inclusion criteria	Patients were eligible for enrollment if they presented within 12 hours after the onset of symptoms, had evidence of acute STEMI on qualifying electrocardiogram (ECG) (≥1mV in ≥2 continuous leads), and, due to anticipated delay to primary PCI, received tenecteplase (TNKase; Genentech, South San Francisco, CA) as the primary mode of reperfusion. Regardless of reperfusion status or haemodynamic stability, a pharmaco-invasive strategy with an angiogram at a PCI-capable hospital within 24 hours of fibrinolysis was mandated. All patients were older than 18 years and provided written informed consent
Exclusion criteria	Major exclusion criteria were any contraindication for the use of clopidogrel or ticagrelor, a need for oral anticoagulation therapy, atrial fibrillation, an increased risk of bradycardia, PCI or coronary artery bypass surgery (CABG) during the previous 3 months, active bleeding or high risk of bleeding based on clinical assessment, known clinically important thrombocytopaenia or anaemia, concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer, and women of child-bearing age. Due to interference with the VerifyNow assay, all patients who received GPIIb/IIIa receptor antagonist before, during or after PCI were excluded from this study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 62.1 (10.2 years); clopidogrel group: 64.1 (14.0 years). Gender (M:F): 107/37. Ethnicity: Ticagrelor group: white (93.4%); clopidogrel group: white (97.1%)
Further population details	
Extra comments	Patients were randomised at the time of diagnostic angiogram and immediately went on to receive the loading dose of their assigned treatment prior to PCI. Patients had already received aspirin and clopidogrel at the time of fibrinolysis
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Antiplatelet - Ticagrelor. 180mg loading dose of ticagrelor followed by 90mg PO twice daily. Duration 30 days. Concurrent medication/care: All patients received 162 to 325mg of aspirin and clopidogrel adjunctive therapy at the time of fibrinolysis as per guidelines. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable 2. Use of GpIIb/IIIa : Not applicable (n=68) Intervention 2: Antiplatelet - Clopidogrel. A loading dose of 300mg clopidogrel followed by 75mg PO daily. Duration 30 days. Concurrent medication/care: All patients received 162 to 325mg of aspirin and clopidogrel adjunctive therapy at the time of fibrinolysis as per guidelines. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable 2. Use of GpIIb/IIIa : Not applicable
Funding	Study funded by industry (This work was supported by an unrestricted investigator-initiated grant from AstraZeneca)

Study	Dehghani 2017[44]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: All-cause mortality at 30 days; Group 1: 1/76, Group 2: 3/68
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Other adverse effects of treatment at 30 days
- Actual outcome for STEMI: Other adverse effects (all events) at 30 days; Group 1: 13/76, Group 2: 12/68
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Other adverse effects (chest pain) at 30 days; Group 1: 3/76, Group 2: 2/68
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Other adverse effects (congestive heart failure) at 30 days; Group 1: 3/76, Group 2: 1/68
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Other adverse effects (hypotension) at 30 days; Group 1: 3/76, Group 2: 2/68
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Other adverse effects (fall) at 30 days; Group 1: 0/76, Group 2: 1/68
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number
- Actual outcome for STEMI: Other adverse effects (musculoskeletal pain) at 30 days; Group 1: 1/76, Group 2: 2/68
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Other adverse effects (rash) at 30 days; Group 1: 0/76, Group 2: 2/68
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study	Dehghani 2017[44]
	Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Other adverse effects (tachyarrhythmia) at 30 days; Group 1: 1/76, Group 2: 1/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Other adverse effects (gingival hives) at 30 days; Group 1: 1/76, Group 2: 0/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Other adverse effects (urinary tract infection) at 30 days; Group 1: 1/76, Group 2: 1/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Breathing adverse effects - Actual outcome for STEMI: Breathing adverse effects (dyspnoea) at 30 days; Group 1: 8/76, Group 2: 3/68 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: missing: ; Group 2 Number missing: Protocol outcome 4: Bradycardic adverse effects - Actual outcome for STEMI: Bradycardic adverse effects (bradycardia) at 30 days; Group 1: 1/76, Group 2: 0/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Complications related to bleeding (including haemorrhagic stroke) - Actual outcome for STEMI: Complications related to bleeding (major, BARC 3-5) at 30 days; Group 1: 2/76, Group 2: 1/68 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Complications related to bleeding (minor, BARC 1-2) at 30 days; Group 1: 9/76, Group 2: 5/68 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study	Dehghani 2017[44]
	Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Stroke - Actual outcome for STEMI: Stroke (any, type not specified) at 30 days; Group 1: 0/76, Group 2: 0/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Need for revascularisation - Actual outcome for STEMI: Need for revascularisation (unplanned revascularisation) at 30 days; Group 1: 0/76, Group 2: 1/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction (myocardial infarction) at 30 days; Group 1: 0/76, Group 2: 1/68; Comments: Myocardial infarction resulted in death Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Unplanned urgent readmission at 30 days for any reason - Actual outcome for STEMI: Unplanned urgent readmission (re-hospitalisation) at 30 days; Group 1: 2/76, Group 2: 4/68 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were similar between groups' although a higher proportion of the ticagrelor group had prior PCI (P = 0.07); Blinding details: 'Antiplatelet assignment was not blinded' ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Quality of life; Early and late stent thrombosis; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Cardiac mortality at 30 days

Study	DISPERSE-2 trial: Cannon 2007[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=661)

Study	DISPERSE-2 trial: Cannon 2007[26]
Countries and setting	Conducted in Multiple countries; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 4-12 weeks follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients experienced ischaemic symptoms of ≥10 minutes duration at rest, with either biochemical marker evidence of myocardial infarction or electrocardiographic evidence of ischaemia
Stratum	UA/NSTEMI: Patients with NSTE-ACS
Subgroup analysis within study	Not applicable
Inclusion criteria	From supplementary appendix: patients aged ≥18 years and hospitalised for NSTE-ACS within the preceding 48 hours. Patients had to have experienced ischaemic symptoms of ≥10 minutes duration at rest, with either biochemical marker evidence of myocardial infarction (defined as troponin T or I, creatine kinase [CK]-MB elevation greater than the local MI decision limit, or if these markers were not available, total CK greater than twice the local MI decision limit) or electrocardiographic evidence of ischaemia, defined as the presence of new or presumably new ST-segment depression ≥0.5mm (0.05mV), transient ST-segment elevation ≥1mm (0.1mV), or T-wave inversion ≥1mm (0.1mV) in 2 or more contiguous leads
Exclusion criteria	From supplementary appendix: persistent ST-segment elevation ≥20 minutes, more than 48 hours from onset of symptoms, index event occurring as a consequence of PCI within the prior 48 hours or performance of PCI within 48 hours of randomisation (i.e. patients had to be randomised pre-PCI); angiography showing no significant coronary stenosis; and any of the following conditions associated with increased risk of bleeding: history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding; gastrointestinal bleeding within the prior 6 months; gastric or duodenal ulcer disease verified by endoscopy or radiographic testing within the prior 6 months; persistent uncontrolled hypertension >180/10 mmHg; any known haemorrhagic disorder; major surgical procedure or trauma within the prior 30 days; or intracranial aneurysm or vascular malformation. Other exclusion criteria included CABG within 3 months before randomisation, non-haemorrhagic stroke within the prior 30 days, active cancer (excluding skin basal cell carcinoma), oral anticoagulation therapy within the prior 7 days or need for chronic oral anticoagulation, chronic daily dosing with nonselective nonsteroidal anti-inflammatory drugs, thrombolytic therapy within the prior 7 days, contraindications for aspirin treatment, concomitant therapy with digoxin or strong cytochrome P450 3A4 inhibitors or cytochrome P450 3A4 substrates with a narrow therapeutic index, known lactose intolerance (due to the excipient in the capsules), serum creatinine level >3.0 mg/dl (265µmol/l), known active liver disease or elevated liver function tests of alanine aminotransferase (ALT) >2x the upper limit of normal or total bilirubin 1.5x the upper limit of normal at the local laboratory, haemoglobin level <10 g/dl (6.2mmol/l), platelet count <100 x 10 to the power of 9/l, and participation in another investigational drug study within 1 month before randomisation

Study	DISPERSE-2 trial: Cannon 2007[26]
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor 90 mg group: 64 (12.1 years); ticagrelor 180mg group: 63 (11.4 years); clopidogrel group: 62 (11.0 years) based on primary safety cohort. Gender (M:F): 632/352 (based on primary safety cohort). Ethnicity: Ticagrelor group (90mg and 180mg groups combined): white 95%, non-white 5%; clopidogrel group: 94%
Further population details	
Extra comments	Patients who had received clopidogrel before randomisation were permitted in the study, but open-label clopidogrel was discontinued after randomisation
Indirectness of population	No indirectness
Interventions	(n=334) Intervention 1: Antiplatelet - Ticagrelor. Patients received 90mg of ticagrelor twice daily. Patients were subrandomised to receive or not to receive an initial loading dose of 270mg. Patients were scheduled to receive 1, 2 or 3 months of study drug, depending on when during the trial period they were enrolled. Patients received aspirin at an initial dose of up to 325mg followed by 75 to 100mg daily. For patients undergoing PCI within 48 hours post-randomisation, an additional 300mg placebo could be administered at the discretion of the treating physician. Duration 4-12 weeks. Concurrent medication/care: Patients received standard medical (anti-ischaemic and antithrombotic) and interventional treatment for ACS, including with or without a glycoprotein IIb/IIIa inhibitor, heparin, beta-blockers and statins. Patients who received clopidogrel before randomisation were permitted in the study, but open-label clopidogrel was discontinued after randomisation and replaced with study drug. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=327) Intervention 2: Antiplatelet - Clopidogrel. Patients received 300mg clopidogrel followed by 75mg once daily. Patients were scheduled to receive 1, 2 or 3 months of study drug, depending on when during the trial period they were enrolled. Patients received aspirin at an initial dose of up to 325mg followed by 75 to 100mg daily. For patients undergoing PCI within 48 hours post-randomisation, an additional 300mg clopidogrel could be administered at the discretion of the treating physician. Duration 4-12 weeks. Concurrent medication/care: Patients received standard medical (anti-ischaemic and antithrombotic) and interventional treatment for ACS, including with or without a glycoprotein IIb/IIIa inhibitor, heparin, beta-blockers and statins. Patients who received clopidogrel before randomisation were permitted in the study, but open-label clopidogrel was discontinued after randomisation and replaced with study drug. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Study funded by industry (AstraZeneca)

Study	DISPERSE-2 trial: Cannon 2007[26]

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for UA/NSTEMI: All-cause mortality (death) at 1 month; Group 1: 6/334, Group 2: 2/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at 30 days
- Actual outcome for UA/NSTEMI: Cardiac mortality (cardiovascular death) at 1 month; Group 1: 6/334, Group 2: 2/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome for UA/NSTEMI: Complications related to bleeding (major) at 1 month; Group 1: 23/334, Group 2: 22/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: 6, Reason: Did not receive at least one dose of study drug - reason not reported; Group 2 Number missing: 0
- Actual outcome for UA/NSTEMI: Complications related to bleeding (minor) at 1 month; Group 1: 9/334, Group 2: 4/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: 6, Reason: Did not receive at least one dose of study drug - reason not reported; Group 2 Number missing: 0

Protocol outcome 4: Stroke
- Actual outcome for UA/NSTEMI: Stroke (any, type not specified) at 1 month; Group 1: 2/334, Group 2: 1/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Re-infarction at 30 days
- Actual outcome for UA/NSTEMI: Re-infarction (myocardial infarction) at 1 month; Group 1: 7/334, Group 2: 11/327
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: Including age, gender, ethnicity for primary safety cohort but not total randomised population;
Group 1 Number missing: ; Group 2 Number missing:

Study	DISPERSE-2 trial: Cannon 2007[26]
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	ETAMI trial: Zeymer 2015[327]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Germany; Setting: In the ambulance or in the emergency department of a PCI hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 30-day follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute STEMI ≤ 12 h defined as angina or equivalent symptoms >30 min; or ST-segment elevation ≥ 2 electrocardiogram leads (≥ 2 mm precordial leads, ≥ 1mm limb leads, or ST depression ≥ 1 mm precordial leads in posterior myocardial infarction
Stratum	STEMI: Intended for PPCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥ 18 years and <75 years; acute STEMI ≤ 12 h defined as angina or equivalent symptoms >30 min; or ST-segment elevation ≥ 2 electrocardiogram leads (≥ 2 mm precordial leads, ≥ 1mm limb leads, or ST depression ≥ 1 mm precordial leads in posterior myocardial infarction; planned PPCI; legal capacity (including ability to understand the nature, scope, and possible consequences of the study participation); and informed consent
Exclusion criteria	Age ≥ 75 years; body weight < 60 kg; thrombolytic therapy within 24 h before randomisation; oral anticoagulation; known haemorrhagic diathesis; history of stroke or transient ischaemic attack; cardiogenic shock; evidence of an active gastrointestinal or urogenital bleeding; major surgery within 6 weeks; contraindication to prasugrel or clopidogrel; severe renal or hepatic insufficiency; contraindication to coronary angiography; planned administration of a glycoprotein (GP) IIb/IIIa inhibitor before angiography; pregnant or nursing (lactating) women; treatment within the last 10 days with clopidogrel, prasugrel, ticlopidine or ticagrelor; uncontrollable hypertension (blood pressure ≥ 200/110 mm Hg in repeated measurements); treatment with NSAIDs; and participation in another clinical or device trial within the previous 30 days
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): prasugrel group: 59 (55-70); clopidogrel group: 640 (49-70). Gender (M:F): 45/17 (ITT population). Ethnicity: Not reported

Study	ETAMI trial: Zeymer 2015[327]
Further population details	
Extra comments	Randomisation to treatment and administration of the drugs occurred before transfer to the catheterisation laboratory, where diagnostic coronary angiography and PPCI with stent implantation was done
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Antiplatelet - Prasugrel. A loading dose of 60 mg prasugrel and 8 tablets of clopidogrel placebo as early as possible. Aspirin (500 mg intravenously or 300 mg orally). Duration 30 days. Concurrent medication/care: The administration of GP IIb/IIIa inhibitors after the diagnostic angiography and prior to or during PPCI was left to the discretion of the treating physician. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=31) Intervention 2: Antiplatelet - Clopidogrel. A loading dose of 600 mg clopidogrel and 6 tablets of prasugrel placebo as early as possible. Aspirin (500 mg intravenously or 300 mg orally). Duration 30 days. Concurrent medication/care: The administration of GP IIb/IIIa inhibitors after the diagnostic angiography and prior to or during PPCI was left to the discretion of the treating physician. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (This study was funded by Daiichi Sankyo and the Stiftung Institut für Herzinfarktforschung Ludwigshafen. Authors also received funding by industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: All-cause mortality at 30 days ; Group 1: 1/31, Group 2: 1/31
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics...did not show any significant differences'; Group 1 Number missing: 1, Reason: Although ITT was applied, for 1 patient 'the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis'. While this referred specially to the analysis of PRI values, the number of participants analysed for clinical events appears to exclude 1 patient; Group 2 Number missing: 0

Protocol outcome 2: Other adverse effects of treatment at 30 days
- Actual outcome for STEMI: Other adverse effects of treatment (cardiogenic shock) at 30 days ; Group 1: 1/31, Group 2: 2/31
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics...did not show any significant differences'; Group 1 Number missing: 1, Reason: Although ITT was applied, for 1 patient 'the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis'. While this referred specially to the analysis of PRI values, the

Study	ETAMI trial: Zeymer 2015[327]
number of participants analysed for clinical events appears to exclude 1 patient; Group 2 Number missing: 0 Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke) - Actual outcome for STEMI: Complications related to bleeding (major or minor, TIMI) at 30 days ; Group 1: 1/31, Group 2: 0/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics...did not show any significant differences'; Group 1 Number missing: 1, Reason: Although ITT was applied, for 1 patient 'the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis'. While this referred specially to the analysis of PRI values, the number of participants analysed for clinical events appears to exclude 1 patient; Group 2 Number missing: 0 Protocol outcome 4: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis at 30 days ; Group 1: 0/31, Group 2: 0/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics...did not show any significant differences'; Group 1 Number missing: 1, Reason: Although ITT was applied, for 1 patient 'the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis'. While this referred specially to the analysis of PRI values, the number of participants analysed for clinical events appears to exclude 1 patient; Group 2 Number missing: 0 Protocol outcome 5: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction at 30 days ; Group 1: 0/31, Group 2: 0/31 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics...did not show any significant differences'; Group 1 Number missing: 1, Reason: Although ITT was applied, for 1 patient 'the actual diagnosis turned out to be pulmonary embolism, and for this patient, study guidance decided that his data should not be included in the intention-to-treat analysis'. While this referred specially to the analysis of PRI values, the number of participants analysed for clinical events appears to exclude 1 patient; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Stroke; Need for revascularisation at 1 year; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Cardiac mortality at 30 days

Study	Han 2019[56]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: Zhengzhou Central Hospital Affiliated to Zhengzhou University

Study	Han 2019[56]
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	STEMI
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who satisfied the diagnostic criteria of STEMI released by WTO, hospitalised within 12 hours after onset, aged below 80 years, and had two or more continuous ST-segment elevation in electrocardiography (chest lead > 0.2 mV and limb lead > 0.1 mV) were included.
Exclusion criteria	Patients who had hepatic and renal insufficiency, immune disease, infectious disease, severe coagulation function, haematological system disease or malignant tumour, could not tolerate surgery, or were allergic to treatment drugs were excluded.
Recruitment/selection of patients	STEMI patients who underwent emergency PCI between January 2016 and December 2017
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 67 (8); clopidogrel group: 67 (8) years. Gender (M:F): 65/56. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Antiplatelet - Ticagrelor. All the patients took 300 mg of aspirin. Patients orally took 180 mg of ticagrelor, then PCI was performed. After PCI, patients were given anti-platelet maintenance treatment, i.e. orally took 100 mg of aspirin once a day and patients were given 90 mg of ticagrelor, twice a day for at least one year. . Duration 12 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear (n=60) Intervention 2: Antiplatelet - Clopidogrel. All the patients took 300 mg of aspirin. Patients orally took 600 mg of clopidogrel, then PCI was performed. After PCI, patients were given anti-platelet maintenance treatment, i.e. orally took 100 mg of aspirin once a day and patients were given 75 mg of ticagrelor, twice a day for at least one year. . Duration 12 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear

Study	Han 2019[56]
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR + ASA versus CLOPIDOGREL + ASA Protocol outcome 1: Cardiac mortality at 30 days - Actual outcome for STEMI: Cardiac mortality at 30 days; Group 1: 1/60, Group 2: 2/60 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Complications related to bleeding (including haemorragic stroke) - Actual outcome for STEMI: Major bleeding at 30 days; Group 1: 0/60, Group 2: 0/60 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for STEMI: Minor bleeding at 30 days; Group 1: 3/60, Group 2: 4/60 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction at 30 days; Group 1: 2/60, Group 2: 4/60 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days ; Non-haemorrhagic stroke; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	ISAR-REACT 5 trial: Schupke 2019[225]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4018)
Countries and setting	Conducted in Germany, Italy; Setting: 23 centres: 21 centres in Germany and 2 centres in Italy
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 12 months

Study	ISAR-REACT 5 trial: Schupke 2019[225]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalization for an acute coronary syndrome (unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI)) with planned invasive strategy; age ≥18 years. For STEMI patients: Chest discomfort suggestive of cardiac ischemia ≥ 20 minutesat rest, within 24 h prior to randomization with 1 of the following ECG features: - ST-segment elevation ≥ 1 mm in ≥ 2 contiguous ECG leads or - new or presumably new left bundle branch block (LBBB) For NSTEMI or unstable angina: Chest discomfort suggestive of cardiac ischemia for ≥ 10minutes at rest within 48 h prior to randomization + 1 of the following criteria: - ST-segment depression ≥ 1 mm in ≥ 1 or 2 contiguous ECGleads or - Troponin T or I or CK-MB greater than the upper limit of normal or - 2 of the following clinical criteria: Age ≥ 60 years, ≥ 3 risk factors for coronary artery disease (arterial hypertension, hypercholesterolemia, current smoker), diabetes mellitus, aspirin use in the past 7 days, severe angina (≥ 2 episodes within the last 24 hours), chronic renal dysfunction, prior MI or CABG, known CAD with ≥ 50% stenosis in ≥ 2 vessels, carotid stenosis ≥ 50% or cerebral revascularization, peripheral artery disease
Exclusion criteria	Examples include the following (full exclusion criteria reported in supplementary material of trial publication: (a) intolerance of or allergy to ticagrelor or prasugrel, (b) history of any stroke, transient ischemic attack or intracranial bleeding, (c) known intracranial neoplasm,intracranial arteriovenous malformation or intracranial aneurysm, (d) active bleeding, clinical findings, that in the judgement of the investigator are associated with an increased risk of bleeding, (e) fibrin-specific fibrinolytic therapy less than 24 h before randomization, non-fibrin-specific fibrinolytic therapy less than 48 h before randomization, (f) known platelet count < 100.000/µLat the time of screening, (g) known anemia (hemoglobin < 10 g/dL) at the time of screening, (h) oral anticoagulation that cannot be safely discontinued for the duration of the study, (i) increased risk of bradycardia events, (j) index event is an acute complication (< 30 days) of PCI, (k) pregnancy
Recruitment/selection of patients	From September 2013 through February 2018
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 64.5 (12) years; Prasugrel group: 64.6 (12.1) years. Gender (M:F): 3062/956. Ethnicity: Not reported
Further population details	

Study	ISAR-REACT 5 trial: Schupke 2019[225]
Extra comments	Diagnosis at admission (mean %): STEMI: 41.2%; NSTEMI: 46.1%; Unstable angina: 12.7%.
Indirectness of population	No indirectness
Interventions	(n=2012) Intervention 1: Antiplatelet - Ticagrelor. Therapy with ticagrelor was started at a loading dose of 180 mg and continued at a maintenance dose of 90 mg twice daily. Patients who were assigned to ticagrelor received the loading dose as soon as possible after randomization. At discharge 94.5% of patients had aspirin (100mg or less). Duration 1 year. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission (Soon as possible after randomisation). 2. Use of GpIIb/IIIa : Not used (Glycoprotein IIb/IIIa were used in 12.3% of the patients who underwent PCI). (n=2006) Intervention 2: Antiplatelet - Prasugrel. Therapy with prasugrel was started at a loading dose of 60 mg and continued at a maintenance dose of 10 mg once per day. A reduced maintenance dose of 5 mg daily was recommended in patients who were 75 years of age or older and in those who had a body weight of less than 60 kg. At discharge 94.5% of patients had aspirin (100mg or less). Duration 1 year. Concurrent medication/care: In the prasugrel group, timing of the initiation of the trial drug depended on the clinical presentation. In patients with ST-segment elevation, prasugrel was to be administered as soon as possible after randomization. In patients who had acute coronary syndromes without ST-segment elevation, administration of the loading dose of prasugrel was postponed until the coronary anatomy was known (with no pretreatment before diagnostic angiography) and before proceeding to percutaneous coronary intervention (PCI) (i.e., before the guidewire crossed the lesion).. Indirectness: No indirectness Further details: 1. Timing of administration: Administration after hospital admission (As soon as possible after randomisation). 2. Use of GpIIb/IIIa : Not used (Glycoprotein IIb/IIIa inhibitors were used in 12.4% of the patients who underwent PCI).
Funding	Academic or government funding (Supported by a grant from the German Center for Cardiovascular Research and Deutsches Herzzentrum Munchen.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR + ASA versus PRASUGREL + ASA

Protocol outcome 1: Cardiac mortality at 1 year
- Actual outcome: Cardiac mortality at 1 year; Group 1: 63/2012, Group 2: 59/2006
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Complications related to bleeding (including haemorragic stroke)

Study	ISAR-REACT 5 trial: Schupke 2019[225]
- Actual outcome: Major bleeding at 1 year; Group 1: 95/1989, Group 2: 80/1773 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 23, Reason: Data on bleeding were analyzed in all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug.; Group 2 Number missing: 233, Reason: Data on bleeding were analyzed in all patients who received at least one dose of the randomly assigned trial drug and were assessed for bleeding events up to 7 days after discontinuation of the trial drug. Protocol outcome 3: Stroke at 1 year - Actual outcome: Stroke (any) at 1 year; Group 1: 22/2012, Group 2: 19/2006 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Early and late stent thrombosis - Actual outcome: Definite or probable stent thrombosis at 1 year; Group 1: 26/2012, Group 2: 20/2006 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: All-cause mortality at 1 year - Actual outcome: All-cause mortality at 1 year; Group 1: 90/2012, Group 2: 73/2006 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Re-infarction at 1 year - Actual outcome: Re-infarction at 1 year; Group 1: 96/2012, Group 2: 60/2006 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days ; Non-haemorrhagic stroke; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Jing 2016[65]
Study type	RCT (Patient randomised; Parallel)

Study	Jing 2016[65]
Number of studies (number of participants)	1 (n=188)
Countries and setting	Conducted in China; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: Unclear duration of follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	STEMI: Treated with primary percutaneous coronary intervention
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were included if they presented with STEMI within 12 hours and planned to receive primary PCI
Exclusion criteria	Patients with the following conditions were excluded: contraindications to clopidogrel or ticagrelor; had thrombolysis within 24 hours; was on glycoprotein IIb/IIIa inhibitors prior to the PCI; was already on oral anticoagulants and needed to continue the medications after the procedure; severe bradycardia or conduction block; severe liver or kidney impairment; active bleeding or coagulation disorder; age >75 years
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Clopidogrel group: 55 (16 years); ticagrelor group: 59 (21 years). Gender (M:F): 112/76. Ethnicity: Chinese
Further population details	
Extra comments	The finally included patients were randomised to receive loading doses of the study treatments. Maintenance doses were given after the primary PCI
Indirectness of population	No indirectness
Interventions	(n=94) Intervention 1: Antiplatelet - Clopidogrel. Loading dose of 600mg clopidogrel and 300mg aspirin. After the primary PCI, a maintenance dose of 75mg clopidogrel was used daily for at least 12 months. Aspirin 100mg daily was used indefinitely. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=94) Intervention 2: Antiplatelet - Ticagrelor. Loading dose of 180mg ticagrelor and 300mg aspirin. After the primary PCI, 90mg ticagrelor was used daily for at least 12 months. Aspirin 100mg daily was used indefinitely. Duration Not reported. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated

Study	Jing 2016[65]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus TICAGRELOR Protocol outcome 1: All-cause mortality at 30 days - Actual outcome for STEMI: All-cause mortality at Not reported; Group 1: 1/94, Group 2: 1/94; Comments: Deaths due to cardiac rupture Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'No significant differences were noticed [in] the demographic and clinic information between the two groups'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Cardiac mortality at 30 days - Actual outcome for STEMI: Cardiac mortality at 30 days; Group 1: 1/94, Group 2: 1/94 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'No significant differences were noticed [in] the demographic and clinic information between the two groups'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Complications related to bleeding (including haemorhragic stroke) - Actual outcome for STEMI: Complications related to bleeding (mild) at 30 days; Group 1: 17/94, Group 2: 23/94 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'No significant differences were noticed [in] the demographic and clinic information between the two groups'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Complications related to bleeding (life-threatening or intracranial haemorrhage (major)) at 30 days; Group 1: 0/94, Group 2: 0/94 Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: 'No significant differences were noticed [in] the demographic and clinic information between the two groups'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Stroke; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	Kitano 2019[76]
Study type	RCT (Patient randomised; Parallel)

Study	Kitano 2019[76]
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in Japan; Setting: Nihon University Itabashi Hospital, Tokyo, Japan
Line of therapy	Not applicable
Duration of study	Intervention time: 8 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: STEMI, NSTEMI and unstable angina was defined as patients who had chest compression with ST-segment deviation or T-wave inversion in electrocardiogram, or elevated levels of cardiac biomarkers such as CKs or cardiac troponins.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with new-onset ACS. ACS included ST-elevation acute myocardial infarction (STEMI), non-ST elevation acute myocardial infarction, and unstable angina.
Exclusion criteria	Due to potential difficulty in acquiring the angioscopic images for the entirely stented segments, subjects whose culprit lesion was left main coronary artery, ostium, or tortuous vessels were excluded. Patients with hemodialysis, severe liver dysfunction, a history of CABG or restenosis after revascularisation, more than two overlapping kinds of stents, who had recovered from cardiopulmonary arrest, or who needed oral anticoagulants were also excluded.
Recruitment/selection of patients	ACS patients admitted to the hospital between December 2014 and November 2016
Age, gender and ethnicity	Age - Mean (SD): Prasugrel group: 66 (13); clopidogrel group: 64 (11) years. Gender (M:F): 64/14. Ethnicity: Not reported
Further population details	
Extra comments	Clinical diagnosis: STEMI (prasugrel: 43.6%; clopidogrel: 53.8%), NSTEMI (prasugrel: 28.2%; clopidogrel: 28.2%), UA (prasugrel: 28.2%; clopidogrel: 17.9%)
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Antiplatelet - Prasugrel. Patients were given 20 mg of prasugrel with a low dose of 162 mg of aspirin (loading dose). After the antiplatelet drug loading, patients underwent PCI with everolimus-eluting stent. Thereafter, the prasugrel group was given a maintenance dose of 100 mg/day of aspirin and 3.75 mg/day of prasugrel until follow-up.. Duration 8 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear (n=39) Intervention 2: Antiplatelet - Clopidogrel. Patients were given 300 mg of clopidogrel with a low dose of

Study	Kitano 2019[76]
	162 mg of aspirin (loading dose). After the antiplatelet drug loading, patients underwent PCI with everolimus-eluting stent. Thereafter, the clopidogrel group was given a maintenance dose of 100 mg/day of aspirin and 75 mg/day of clopidogrel until follow-up.. Duration 8 months. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Study funded by industry (Study was financially supported by Daiichi Sankyo Co. Ltd (Tokyo, Japan) as an investigator-initiated research.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL Protocol outcome 1: Non-haemorrhagic stroke - Actual outcome: Stroke (any, type not specified) at 1 year; Group 1: 1/38, Group 2: 1/37 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Withdrew consent Protocol outcome 2: Need for revascularisation at 1 year - Actual outcome: Need for revascularisation at 1 year; Group 1: 2/38, Group 2: 2/37 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Withdrew consent Protocol outcome 3: All-cause mortality at 1 year - Actual outcome: All-cause mortality at 1 year; Group 1: 2/38, Group 2: 1/37 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Withdrew consent; Group 2 Number missing: 2, Reason: Withdrew consent	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days ; Cardiac mortality at 30 days ; Complications related to bleeding (including haemorragic stroke); Early and late stent thrombosis; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Laine 2014[84]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in France; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: Unclear duration of follow-up. The primary endpoint was measured at 6 and 18 hours post loading dose
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall: Diabetic patients undergoing an invasive strategy (but who did not have a cardiac arrest)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with diabetes mellitus admitted for ACS were screened. Only those selected for an invasive strategy were eligible. In the present study only those who underwent PCI and agreed to participate in the study were included.
Exclusion criteria	Cardiac arrest, cardiogenic shock, contraindications to antiplatelet therapy, a platelet count <100 G/l, history of bleeding diathesis, bleeding, concurrent severe illness with expected survival of <1 month, surgery within one month or scheduled in the year, coumadin or other oral anticoagulant therapy, atrial fibrillation, current clopidogrel, ticagrelor or prasugrel treatment, pregnancy, liver failure, fibrinolytics, previous stroke/transient ischaemic attack, weight <60kg, age over 75 years old, platelet count <100,000/ml, haematocrit <30%, creatinin clearance <30ml/minute (min), severe hepatic dysfunction, use of strong CYP3A, inhibitors or inducers, increased risk of bradycardia or severe chronic obstructive pulmonary disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Ticagrelor group: 64.8 (8.9 years); prasugrel group: 62.8 (8.2 years). Gender (M:F): 76/24. Ethnicity: Not reported
Further population details	
Extra comments	Diabetes was defined as a history of diabetes mellitus under stable chronic medical therapy for at least three months. Only patients selected for an invasive strategy were eligible; they received aspirin on admission and after randomisation were assigned to treatment groups
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Antiplatelet - Ticagrelor. Patients in both groups received a 250mg intravenous loading dose of aspirin on admission followed by 75mg per os daily indefinitely. After randomisation, patients received 180mg ticagrelor as a loading dose. The maintenance dose of ticagrelor was 90mg twice daily. Duration Unclear duration of follow-up. Concurrent medication/care: Glycoprotein 2b/3a inhibitors were not

Study	Laine 2014[84]
	used, and all patients received a 4,000 UI bolus of heparin intravenously during PCI. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=50) Intervention 2: Antiplatelet - Prasugrel. Patients in both groups received a 250mg intravenous loading dose of aspirin on admission followed by 75mg per os daily indefinitely. After randomisation, patients received 60mg prasugrel as a loading dose. The maintenance dose of prasugrel was 10mg daily. Duration Unclear duration of follow-up. Concurrent medication/care: Glycoprotein 2b/3a inhibitors were not used, and all patients received a 4,000 UI bolus of heparin intravenously during PCI. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable
Funding	Other (Supported by a grant from the Assistance-Publique Hopitaux de Marseille)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus PRASUGREL

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome: All-cause mortality in hospital (at 30 days); Group 1: 0/50, Group 2: 1/50; Comments: Death due to cardiogenic shock following ST elevation myocardial infarction
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There was no difference in baseline characteristics between the two groups of patients' although a higher proportion of the ticagrelor group received aspirin, beta blockers and statins on admission; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at 30 days
- Actual outcome: Cardiac mortality in hospital (at 30 days); Group 1: 0/50, Group 2: 1/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There was no difference in baseline characteristics between the two groups of patients' although a higher proportion of the ticagrelor group received aspirin, beta blockers and statins on admission; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome: Complications related to bleeding (major, BARC ≥3) in hospital (at 30 days); Group 1: 0/50, Group 2: 0/50
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There was no difference in baseline characteristics between the two groups of patients' although a higher proportion of the ticagrelor group received aspirin, beta blockers and statins on admission; Group 1 Number missing: ; Group 2 Number missing:

Study	Laine 2014[84]
Protocol outcome 4: Stroke - Actual outcome: Stroke (any, type not specified) in hospital (at 30 days); Group 1: 0/50, Group 2: 0/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There was no difference in baseline characteristics between the two groups of patients' although a higher proportion of the ticagrelor group received aspirin, beta blockers and statins on admission; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Re-infarction at 30 days - Actual outcome: Re-infarction (myocardial infarction) in hospital (at 30 days); Group 1: 0/50, Group 2: 1/50 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'There was no difference in baseline characteristics between the two groups of patients' although a higher proportion of the ticagrelor group received aspirin, beta blockers and statins on admission; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	Lee 2015[93]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=39)
Countries and setting	Conducted in South Korea; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days follow-up
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	STEMI: Undergoing PCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Not reported
Exclusion criteria	Age <20 or >80 years or body weight <50kg; previous administration of any P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor); history of stroke or transient ischaemic attack; gastrointestinal bleeding within

Study	Lee 2015[93]
	previous 6 months, bleeding diathesis, platelet count <100,000/mm³ or haemoglobin <10g/dl; known chronic renal insufficiency (serum creatine >2.5mg/dl) or hepatic dysfunction (serum liver enzyme or bilirubin >3-fold higher than the normal limit); and known severe chronic obstructive pulmonary disease or bradycardia
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Prasugrel group: 55 (10 years); ticagrelor group: 55 (11 years). Gender (M:F): 35/4. Ethnicity: Korean
Further population details	
Extra comments	Glycoprotein IIb/IIIa inhibitors intracoronary only were permitted for use at the discretion of the attending physician. Patients were randomised to study treatments in the emergency room prior to arrival at the cardiac catheterisation room
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Antiplatelet - Prasugrel. A loading dose of 60mg prasugrel in combination with 300mg aspirin in the emergency room prior to arrival at the cardiac catheterisation room. Prasugrel 10mg 4 times daily was administered continuously during the follow-up as the maintenance dose. Duration 30 days. Concurrent medication/care: Glycoprotein IIb/IIIa inhibitors intracoronary only were permitted for use at the discretion of the attending physician. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=20) Intervention 2: Antiplatelet - Ticagrelor. A loading dose of 180mg ticagrelor in combination with 300mg aspirin in the emergency room prior to arrival at the cardiac catheterisation room. Ticagrelor 90mg twice daily was administered continuously during the follow-up as the maintenance dose. Duration 30 days. Concurrent medication/care: Glycoprotein IIb/IIIa inhibitors intracoronary only were permitted for use at the discretion of the attending physician. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Academic or government funding (This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Clinical Trials Global Initiative (KCGI), funded by the Ministry of Health & Welfare, funded by the Ministry of Education, Science and Technology)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus TICAGRELOR

Protocol outcome 1: Other adverse effects of treatment at 30 days
- Actual outcome for STEMI: Other adverse effects (drug side effects including dyspnoea and ventricular pauses) at 30 days; Group 1: 0/19, Group 2: 0/20
Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study	Lee 2015[93]
- Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well-matched for all baseline characteristics, including age, sex, body weight, body mass index, cardiovascular risk factors, vital signs and renal function'. Baseline laboratory and procedural characteristics were also similar between groups; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Other adverse effects (moderate chronic kidney disease) at 30 days; Group 1: 0/19, Group 2: 1/20 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well-matched for all baseline characteristics, including age, sex, body weight, body mass index, cardiovascular risk factors, vital signs and renal function'. Baseline laboratory and procedural characteristics were also similar between groups; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Cardiac mortality at 30 days ; Complications related to bleeding (including haemorrhagic stroke); Stroke; Need for revascularisation at 1 year; Early and late stent thrombosis; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Li 2018[100]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=653)
Countries and setting	Conducted in China; Setting: Jinan Central Hospital Affiliated Shandong University, which is a Chest Pain Centre in China.
Line of therapy	Not applicable
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: STEMI was defined as ST-segment elevation in at least two contigous leads or a new left bundle-branch block, and an increase in at least one value above the 99th percentile upper reference limit.
Stratum	STEMI
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ≥18 years of age with documented STEMI undergoing successful primary PCI.
Exclusion criteria	A history of therapy with oral anticoagulant within 12 months; platelet count < 100,000/mm^3; creatinine clearance <30 mL/min; pregnancy; bleeding diathesis; a history of malignant tumor with life expectancy <12 months; significant infection with temperature >38C.

Study	Li 2018[100]
Recruitment/selection of patients	Patients undergoing successful primary PCI were enrolled between January 2014 and March 2017.
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 60 (11); clopidogrel group: 63 (13) years. Gender (M:F): 346/96. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=329) Intervention 1: Antiplatelet - Ticagrelor. Before primary PCI, combination of a 300 mg loading dose of aspirin, a loading dose of 180 mg ticagrelor was given. The patients received ticagrelor 90 twice a day for at least 12 months, along with aspirin 100 mg daily.. Duration 12 months. Concurrent medication/care: Primary PCI with drug-eluting stents. Other drugs (i.e. beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker, and proton pump inhibitors) decisions were made by the treating physicians in accordance with the practice guideline recommendations and the clinical status of patients.. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear (n=324) Intervention 2: Antiplatelet - Clopidogrel. Before primary PCI, combination of a 300 mg loading dose of aspirin, a loading dose of 600 mg clopidogrel was given. The patients received clopidogrel 75 twice a day for at least 12 months, along with aspirin 100 mg daily.. Duration 12 months. Concurrent medication/care: Primary PCI with drug-eluting stents. Other drugs (i.e. beta-blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker, and proton pump inhibitors) decisions were made by the treating physicians in accordance with the practice guideline recommendations and the clinical status of patients.. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Academic or government funding (Grant from Shandong Province Science & Technology Department Plan Project grant)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR + ASA versus CLOPIDOGREL + ASA

Protocol outcome 1: Cardiac mortality at 1 year
- Actual outcome for STEMI: Cardiac mortality at 1 year; Group 1: 3/161, Group 2: 8/281
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local

Study	Li 2018[100]
	unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. Protocol outcome 2: Complications related to bleeding (including haemorragic stroke) - Actual outcome for STEMI: Major bleeding at 1 year; Group 1: 2/161, Group 2: 4/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. - Actual outcome for STEMI: Minor bleeding at 1 year; Group 1: 28/161, Group 2: 24/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. Protocol outcome 3: Non-haemorrhagic stroke - Actual outcome for STEMI: Stroke (ischemic stroke) at 1 year; Group 1: 1/161, Group 2: 3/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. Protocol outcome 4: Need for revascularisation at 1 year - Actual outcome for STEMI: Revascularisation at 1 year; Group 1: 4/161, Group 2: 28/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-

Study	Li 2018[100]
hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. Protocol outcome 5: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis at 1 year; Group 1: 0/161, Group 2: 4/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up. Protocol outcome 6: Re-infarction at 1 year - Actual outcome for STEMI: Re-infarction at 1 year; Group 1: 0/161, Group 2: 6/281 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 168, Reason: 152 patients switched to clopidogrel: few switches in-hospital (most frequent cause of switching in-hospital was dyspnea), majority of switching occurred in the first month due to financial burden and local unavailability. Other reasons for missing data included death in hospital, lost to follow-up. ; Group 2 Number missing: 43, Reason: 8 patients switched to ticagrelor: 4 switches in-hospital (most frequent cause of switching in-hospital was dyspnea), 4 of the switches occurred in the first month. Reasons for switches were due to unexpected rehospitalisation for angina and stent thrombosis (n=4), physicians' suggestion (n=3), and gene detection (n=1). Other reasons for missing data included death in hospital, lost to follow-up.	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days ; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	PHILO trial: Goto 2015[53]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=801)

Study	PHILO trial: Goto 2015[53]
Countries and setting	Conducted in Multiple countries; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months follow-up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall: Planned PCI
Subgroup analysis within study	Not applicable:
Inclusion criteria	Hospitalised for ST or non-ST segment elevation with onset of symptoms during the previous 24 hours (cardiac ischaemic symptoms of ≥10 minutes duration at rest) and planned PCI
Exclusion criteria	Any contraindication against the use of clopidogrel; active bleeding or a history of bleeding; fibrinolytic therapy within 24 hours before randomisation; need for oral anticoagulation therapy; increased risk of bradycardia; and concomitant therapy with a strong CYP3A inhibitor or inducer
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 67 (12 years); clopidogrel group: 66 (11 years). Gender (M:F): Define. Ethnicity: Asian (Chinese, Japanese, Korean and unknown ethnic groups)
Further population details	
Extra comments	Patients received the study drugs directly after randomisation except treatment with clopidogrel and ticagrelor was delayed in patients undergoing CABG. The clopidogrel dosage was also adjusted for patients who had already received a loading dose or who were already taking maintenance doses of clopidogrel or ticlopidine for ≥5 days prior to randomisation
Indirectness of population	No indirectness
Interventions	(n=401) Intervention 1: Antiplatelet - Ticagrelor. An initial loading dose of 180mg ticagrelor, followed by 90mg twice daily and once daily matching placebo tablets. In patients undergoing CABG, the blinded study drug (eg. active drug or placebo) was withheld for 24-72 hours in the ticagrelor group. All patients received aspirin at a dose of 75-100mg once daily (a loading dose of up to 330mg was permitted) unless aspirin was contraindicated or poorly tolerated. Duration 12 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=400) Intervention 2: Antiplatelet - Clopidogrel. Patients who were clopidogrel naive received an initial loading dose of 300mg clopidogrel orally or matching placebo, then 75mg once daily and placebo capsules twice daily thereafter. Patients in the clopidogrel group who had already received a loading dose or who were already taking maintenance doses of clopidogrel or ticlopidine for ≥5 days prior to randomisation were

Study	PHILO trial: Goto 2015[53]
	given clopidogrel 75mg once daily plus placebo capsules twice daily. All patients received aspirin at a dose of 75-100mg once daily (a loading dose of up to 330mg was permitted) unless aspirin was contraindicated or poorly tolerated. Duration 12 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other author(s) funded by industry (Medical writing support was funded by AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: Other adverse effects of treatment
- Actual outcome: Other adverse effects (any, excluding bleeding) at 1 year; Group 1: 327/401, Group 2: 337/400; Comments: Note that % reported appears to be different to number of events/number analysed
Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Breathing adverse effects (dyspnoea) at 1 year; Group 1: 22/401, Group 2: 9/400; Comments: Note that % reported appears to be different to number of events/number analysed
Risk of bias: All domain – Very High, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Bradycardic adverse effects
- Actual outcome: Bradycardic adverse effects (bradycardia) at 1 year; Group 1: 11/401, Group 2: 9/400; Comments: Note that % reported appears to be different to number of events/number analysed
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded

Study	PHILO trial: Goto 2015[53]
data; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Bradycardic adverse effects (ventricular pauses ≥3 seconds) at 1 year; Group 1: 0/401, Group 2: 1/400; Comments: Note that % reported appears to be different to number of events/number analysed Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Cardiac mortality at 1 year - Actual outcome: Cardiac mortality at 1 year; Group 1: 9/401, Group 2: 7/400; Comments: Hazard ratio: 1.28 (95% CI 0.48-3.45) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Complications related to bleeding (including haemorragic stroke) - Actual outcome: Complications related to bleeding (major, PLATO-defined) at 1 year; Group 1: 40/401, Group 2: 26/400; Comments: Note that % reported appears to be different to number of events/number analysed. Hazard ratio: 1.54 (95% CI 0.94-2.53) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (minor, PLATO-defined) at 1 year; Group 1: 59/401, Group 2: 35/400; Comments: Note that % reported appears to be different to number of events/number analysed. Hazard ratio: 1.75 (95% CI 1.15-2.67) Risk of bias: All domain – Very High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing:	

Study	PHILO trial: Goto 2015[53]
Protocol outcome 5: Stroke - Actual outcome: Stroke (any, type not specified) at 1 year; Group 1: 9/401, Group 2: 6/400; Comments: Hazard ratio: 1.50 (0.54-4.23) Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: All-cause mortality at 1 year - Actual outcome: All-cause mortality at 1 year; Group 1: 10/401, Group 2: 7/400; Comments: Hazard ratio: 1.42 (95% CI 0.54-3.74) Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Re-infarction at 1 year - Actual outcome: Re-infarction (myocardial infarction, excluding silent myocardial infarction) at 1 year; Group 1: 24/401, Group 2: 15/400; Comments: Hazard ratio: 1.63 (95% CI 0.85-3.11) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Ticagrelor group highlighted to have a greater prevalence of coronary risk factors, higher proportion ≥75 years, with a history of CABG, and with positive troponin I levels and ST depression ≥1mm during the index event; clopidogrel group highlighted to have a higher proportion with a history of TIA; Blinding details: An independent, external clinical endpoint committee reviewed and adjudicated the efficacy and bleeding endpoints; an independent data and safety monitoring board monitored the trial and had access to the unblinded data; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; Early and late stent thrombosis; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=18,624)

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])
Countries and setting	Conducted in Multiple countries; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute coronary syndrome with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. For patients who had an acute coronary syndrome without ST-segment elevation, at least two of the following three criteria had to be met: ST-segment changes on electrocardiography, indicating ischaemia; a positive test of a biomarker, indicating myocardial necrosis; or one of several risk factors (age ≥60 years; previous myocardial infarction or coronary artery bypass grafting (CABG); coronary artery disease with stenosis of ≥50% in at least two vessels; previous ischaemic stroke, transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of <60ml per minute per 1.73m² of body surface area). For patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1mV in at least two contiguous leads or a new left bundle-branch block, and the intention to perform primary PCI
Stratum	Overall: Majority underwent PCI (ticagrelor group: 64.1%; clopidogrel group: 64.6%)
Subgroup analysis within study	Not stratified but pre-specified: The consistency of effects on efficacy and safety end points was explored in 25 prespecified subgroups (including non-invasively managed patients) and 8 post hoc subgroups
Inclusion criteria	Acute coronary syndrome with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. For patients who had an acute coronary syndrome without ST-segment elevation, at least two of the following three criteria had to be met: ST-segment changes on electrocardiography, indicating ischaemia; a positive test of a biomarker, indicating myocardial necrosis; or one of several risk factors (age ≥60 years; previous myocardial infarction or coronary artery bypass grafting (CABG); coronary artery disease with stenosis of ≥50% in at least two vessels; previous ischaemic stroke, transient ischaemic attack, carotid stenosis of at least 50%, or cerebral revascularisation; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of <60ml per minute per 1.73m² of body surface area). For patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1mV in at least two contiguous leads or a new left bundle-branch block, and the intention to perform primary PCI
Exclusion criteria	Major exclusion criteria were any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 hours before randomisation, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer
Recruitment/selection of patients	Not reported

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])
Age, gender and ethnicity	Age - Other: Ticagrelor group median: 62 years (IQR or range not reported); Clopidogrel group median: 62 years (IQR or range not reported). Gender (M:F): 13336/5288. Ethnicity: Ticagrelor group: white (91.8%), black (1.2%), asian (5.8%), other (1.2%); Clopidogrel group: white (91.6%), black (1.2%), asian (6.0%), other (1.2%)
Further population details	
Extra comments	Patients underwent PCI after randomisation. Those in the clopidogrel group who had not received an open-label loading dose and had not been taking clopidogrel for at least 5 days before randomisation received a 300-mg loading dose followed by a dose of 75mg daily
Indirectness of population	No indirectness
Interventions	(n=9333) Intervention 1: Antiplatelet - Ticagrelor. Ticagrelor was given in a loading dose of 180mg followed by a dose of 90mg twice daily. Patients undergoing PCI after randomisation received, in a blind fashion, an additional dose of ticagrelor at the time of PCI: 90mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomisation. In patients undergoing CABG, it was recommended that the study drug be withheld - in the ticagrelor group, for 24 to 72 hours. Duration 12 months. Concurrent medication/care: All patients received acetylsalicyclic acid (aspirin) at a dose of 75 to 100mg daily unless they could not tolerate the drug. For those who had not been receiving aspirin, 325mg was the preferred loading dose; 325mg was also permitted as the daily dose for 6 months after stent placement. Indirectness: No indirectness Further details: 1. Timing of administration: Administration after hospital admission: Not applicable (n=9291) Intervention 2: Antiplatelet - Clopidogrel. Patients in the clopidogrel group who had not received an open-label loading dose and had not been taking clopidogrel for at least 5 days before randomisation received a 300-mg loading dose followed by a dose of 75mg daily. Others in the clopidogrel group continued to receive a maintenance dose of 75mg daily. Patients undergoing PCI after randomisation received, in a blind fashion, an additional dose of clopidogrel at the time of PCI: 300mg of clopidogrel, at the investigator's discretion. In patients undergoing CABG, it was recommended that the study drug be withheld - in the clopidogrel group, for 5 days. Duration 12 months. Concurrent medication/care: All patients received acetylsalicyclic acid (aspirin) at a dose of 75 to 100mg daily unless they could not tolerate the drug. For those who had not been receiving aspirin, 325mg was the preferred loading dose; 325mg was also permitted as the daily dose for 6 months after stent placement. Indirectness: No indirectness Further details: 1. Timing of administration: Administration after hospital admission: Not applicable
Funding	Other (Supported by AstraZeneca)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL	

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

ACS (with/without revascularisation)

Protocol outcome 1: All-cause mortality at 30 days *[unpublished data]*
- Actual outcome: All-cause mortality at 30 days; Group 1: 179/9235, Group 2: 212/9186;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 2: All-cause mortality at 1 year
- Actual outcome: All-cause mortality at 1 year; Group 1: 399/9333, Group 2: 506/9291; Comments: Hazard ratio (95% CI): 0.78 (0.69-0.89)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Cardiac mortality
- Actual outcome: Cardiac mortality (death from vascular causes) at 1 year; Group 1: 353/9333, Group 2: 442/9291; Comments: Hazard ratio for ticagrelor group: 0.79 (0.69-0.91)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Re-infarction at 30 days *[unpublished data]*
- Actual outcome: Re-infarction at 30 days; Group 1: 121/9235, Group 2: 165/9186;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 5: Re-infarction at 1 year
- Actual outcome: Re-infarction (myocardial infarction) at 1 year; Group 1: 504/9333, Group 2: 593/9291; Comments: Hazard ratio (95% CI): 0.84 (0.75 to 0.95)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Complications related to bleeding at 30 days *[unpublished data]*
- Actual outcome: Complications related to bleeding (major) at 30 days; Group 1: 645/9235, Group 2: 642/9186;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 7: Complications related to bleeding at 1 year
- Actual outcome: Complications related to bleeding (major or minor) at 1 year; Group 1: 1339/9235, Group 2: 1215/9186; Comments: Hazard or odds ratio for ticagrelor group: 1.11 (1.03-1.20)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported
- Actual outcome: Complications related to bleeding (major) at 1 year; Group 1: 961/9235, Group 2: 929/9186; Comments: Hazard or odds ratio for ticagrelor group: 1.04 (0.95-1.13)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported
- Actual outcome: Complications related to bleeding (minor) at 1 year; Group 1: 378/9235, Group 2: 286/9186
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 8: Stroke at 30 days *[unpublished data]*
- Actual outcome: Stroke at 30 days; Group 1: 57/9235, Group 2: 43/9186;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

Protocol outcome 9: Stroke at 1 year
- Actual outcome: Stroke (ischaemic) at 1 year; Group 1: 96/9333, Group 2: 91/9291
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Stroke (haemorrhagic) at 1 year; Group 1: 23/9333, Group 2: 13/9291
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Stroke (unknown) at 1 year; Group 1: 10/9333, Group 2: 2/9291
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 10: Breathing adverse effects
- Actual outcome: Breathing adverse effects (dyspnoea, any) at 1 year; Group 1: 1270/9235, Group 2: 721/9186; Comments: Hazard or odds ratio for ticagrelor group: 1.84 (1.68-2.02)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 11: Other adverse effects of treatment
- Actual outcome: Other adverse effects (heart block) at 1 year; Group 1: 67/9235, Group 2: 66/9186
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported
- Actual outcome: Other adverse effects (syncope) at 1 year; Group 1: 100/9235, Group 2: 76/9186
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 12: Bradycardic adverse effects

- Actual outcome: Bradycardic adverse effects (ventricular pauses ≥3 seconds) at 30 days; Group 1: 21/985, Group 2: 17/1006
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported
- Actual outcome: Bradycardic adverse effects (bradycardia) at 1 year; Group 1: 409/9235, Group 2: 372/9186
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported
- Actual outcome: Bradycardic adverse effects (pacemaker insertion) at 1 year; Group 1: 82/9235, Group 2: 79/9186
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: 98, Reason: Not reported; Group 2 Number missing: 105, Reason: Not reported

Protocol outcome 13: Early and late stent thrombosis

- Actual outcome: Stent thrombosis (probable or definite) at 1 year; Group 1: 118/5640, Group 2: 158/5649; Comments: Hazard ratio for ticagrelor group: 0.77 (0.62-0.95)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'The two treatment groups were balanced with regard to all baseline characteristics and non-study medications and procedures'; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

<u>Substrata: UA/STEMI + revascularisation</u>

Protocol outcome 1: All-cause mortality

- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: All-cause mortality (death) at 30 days; HR; 0.64 (95%CI 0.44 to 0.92, Comments: Kaplan-Meier estimate. Total N: 6218);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

2 Number missing:
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: All-cause mortality at 1 year; HR; 0.75 (95%CI 0.53 to 1.07, Comments: Kaplan-Meier estimates. Total N: 5648);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality

- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Cardiac mortality (cardiovascular death including vascular and unknown deaths) at 30 days; HR; 0.67 (95%CI 0.43 to 1.02, Comments: Kaplan-Meier estimate. Total N: 6218);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Cardiac mortality (cardiovascular death, including vascular and unknown deaths) at 1 year; HR; 0.76 (95%CI 0.52 to 1.13, Comments: Kaplan-Meier estimates. Total N: 5648);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding

- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Complications related to bleeding (major) at 30 days; HR; 1.14 (95%CI 0.84 to 1.56, Comments: Kaplan-Meier estimate. Total N: 4958);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Complications related to bleeding (major or minor) at 30 days; HR; 1.20 (95%CI 0.92 to 1.56, Comments: Kaplan-Meier estimate. Total N: 4797);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Complications related to bleeding (major) at 1 year; HR; 1.10 (95%CI 0.84 to 1.44, Comments: Kaplan-Meier estimates. Total N: 4983);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Complications related to bleeding (major or minor) at 1 year; HR; 1.22 (95%CI 0.97 to 1.54, Comments: Kaplan-Meier estimates. Total N: 4842);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Stroke
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Stroke (any, type not specified) at 30 days; HR; 1.14 (95%CI 0.54 to 2.4, Comments: Kaplan-Meier estimate. Total N: 6188);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Stroke (any, type not specified) at 1 year; HR; 1.18 (95%CI 0.6 to 2.34, Comments: Kaplan-Meier estimates. Total N: 5632);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Re-infarction
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Re-infarction at 30 days; HR; 0.86 (95%CI 0.63 to 1.16, Comments: Kaplan-Meier estimate. Total N: 5934);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for UA/NSTEMI: NSTE-ACS and revascularisation subgroup: Re-infarction (myocardial infarction excluding silent) at 1 year; HR; 0.90 (95%CI 0.68 to 1.21, Comments: Kaplan-Meier estimates. Total N: 5438);

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Substrata: UA/STEMI + no revascularisation

Protocol outcome 1: All-cause mortality

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: All-cause mortality (death) at 30 days; HR; 0.84 (95%CI 0.63 to 1.11, Comments: Kaplan-Meier estimate. Total N: 4514);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: All-cause mortality at 1 year; HR; 0.73 (95%CI 0.57 to 0.93, Comments: Kaplan-Meier estimates. Total N: 5217);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Cardiac mortality (cardiovascular death including vascular and unknown deaths) at 30 days; HR; 0.84 (95%CI 0.62 to 1.14, Comments: Kaplan-Meier estimate. Total N: 4514);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Complications related to bleeding (including haemorrhagic stroke)

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Cardiac mortality (cardiovascular death, including vascular and unknown deaths) at 1 year; HR; 0.75 (95%CI 0.58 to 0.98, Comments: Kaplan-Meier estimates. Total N: 5217);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

2 Number missing:

Protocol outcome 3: Complications related to bleeding

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Complications related to bleeding (major or minor) at 30 days; HR; 1.16 (95%CI 0.92 to 1.46, Comments: Kaplan-Meier estimate. Total N: 3899);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Complications related to bleeding (major) at 30 days; HR; 1.18 (95%CI 0.91 to 1.54, Comments: Kaplan-Meier estimate. Total N: 3964);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Complications related to bleeding (major or minor) at 1 year; HR; 1.07 (95%CI 0.91 to 1.25, Comments: Kaplan-Meier estimates. Total N: 4847);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Complications related to bleeding (major) at 1 year; HR; 1.05 (95%CI 0.88 to 1.26, Comments: Kaplan-Meier estimates. Total N: 4931);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Stroke

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Stroke (any, type not specified) at 30 days; HR; 0.84 (95%CI 0.5 to 1.4, Comments: Kaplan-Meier estimate. Total N: 4503);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Stroke (any, type not specified) at 1 year; HR; 0.92 (95%CI 0.58 to 1.46,

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

Comments: Kaplan-Meier estimates. Total N: 5209);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Re-infarction at 30 days

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Re-infarction at 30 days; HR; 0.89 (95%CI 0.68 to 1.17, Comments: Kaplan-Meier estimate. total N: 4479);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Re-infarction at 1 year

- Actual outcome for UA/NSTEMI: NSTE-ACS and no revascularisation subgroup: Re-infarction (myocardial infarction excluding silent) at 1 year; HR; 0.94 (95%CI 0.75 to 1.17, Comments: Kaplan-Meier estimates. Total N: 5201);

Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures ; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

<u>Substrata: STEMI + revascularisation</u>

Protocol outcome 1: All-cause mortality
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: All-cause mortality at 1 year; Group 1: 175/3752, Group 2: 216/3792; Comments: HR (95% CI): 0.82 (0.67 to 1.00)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at 30 days
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Cardiac mortality (cardiovascular death) at 1 year; Group 1: 159/3752, Group 2:

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

195/3792; Comments: HR (95% CI): 0.83 (0.67 to 1.02)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Breathing adverse effects
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Breathing adverse effects (dyspnoea) at 1 year; Group 1: 468/3719, Group 2: 314/3752
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Bradycardic adverse effects
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Bradycardic adverse effects (pacemaker placement) at 1 year; Group 1: 50/3719, Group 2: 38/3752
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Bradycardic adverse effects (bradycardia) at 1 year; Group 1: 173/3719, Group 2: 179/3752
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Other adverse effects of treatment
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Other adverse effects (heart block) at 1 year; Group 1: 38/3719, Group 2: 34/3752
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Other adverse effects (syncope) at 1 year; Group 1: 39/3719, Group 2: 28/3752
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])

Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Complications related to bleeding
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Complications related to bleeding (major) at 1 year; Group 1: 301/3719, Group 2: 311/3752; Comments: HR (95% CI): 0.98 (0.83 to 1.14)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Complications related to bleeding (major and minor) at 1 year; Group 1: 439/3719, Group 2: 421/3752; Comments: HR (95% CI): 1.05 (0.92 to 1.21)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Complications related to bleeding (minor) at 1 year; Group 1: 160/3719, Group 2: 129/3752; Comments: HR (95% CI): 1.26 (1.00 to 1.59); note that total number of events for 'major' and 'minor' bleeding is not the same as 'major and minor' total events
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Stroke
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Stroke (any) at 1 year; Group 1: 56/3752, Group 2: 35/3792; Comments: HR (95% CI): 1.63 (1.07 to 2.48)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Stroke (non-haemorrhagic) at 1 year; Group 1: 42/3752, Group 2: 27/3792; Comments: HR (95% CI): 1.58 (0.97 to 2.56)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group

Study (subsidiary papers)	PLATO trial: Wallentin 2009[284] (Lindholm 2014[103], Steg 2010[247])
2 Number missing: Protocol outcome 8: Early and late stent thrombosis - Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Stent thrombosis (definite or probable) at 1 year; Group 1: 73/3752, Group 2: 101/3792; Comments: HR (95% CI): 0.74 (0.55 to 1.00) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 9: Re-infarction at 30 days - Actual outcome for STEMI: STE-ACS and planned PPCI subgroup: Re-infarction (myocardial infarction excluding silent myocardial infarction) at 1 year; Group 1: 159/3752, Group 2: 201/3792; Comments: HR (95% CI): 0.80 (0.65 to 0.98) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: Similar for baseline characteristics, non-study medications and procedures; Blinding details: 'An independent data and safety monitoring board monitored the trial and had access to the unblinded data'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; Need for revascularisation at 1 year

Study	PRAGUE-18 trial: Motovska 2016[119]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1230)
Countries and setting	Conducted in Czech Republic; Setting: In hospital, with telephone visit on day 30
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days follow-up

Study	PRAGUE-18 trial: Motovska 2016[119]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: A diagnosis of acute myocardial infarction from the clinical presentation and an ECG finding of ST-segment elevation on 2 related leads at a minimum by >1mm, ST-segment depression on 3 leads at a minimum by >2mm, or a new bundle branch block
Stratum	Overall: Undergoing coronary angiography with or without PCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute myocardial infarction indicated for emergent (within 120 minutes of admission to a cardiac centre) coronary angiography with or without PCI and a signed informed consent
Exclusion criteria	History of stroke, serious bleeding within the past 6 months, indication for long-term oral anticoagulation therapy, administration of clopidogrel ≥300mg or any other antiplatelet medication (except aspirin and a lower dose of clopidogrel) before randomisation, aged >75 years with a body weight <60kg (ie. the presence of both parameters was an exclusion criterion), moderate or severe hepatic function disorder, concomitant treatment with a strong CYP3A4 inhibitor, and known hypersensitivity to prasugrel or ticagrelor
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Prasugrel group: 61.8 (42.7-78.7 years); Ticagrelor group: 61.8 (44.6-79.8 years). Gender (M:F): 928/302. Ethnicity: Not reported
Further population details	
Extra comments	Haemodynamic instability was not an exclusion criterion. Patients were randomised to treatment groups after signing the informed consent, immediately on hospital arrival (which, as a rule, was directly to the catheterisation laboratory or, in exceptional cases, to the coronary care unit). Administration of the loading dose was recommended immediately after patients signed the informed consent. In individual cases, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI
Indirectness of population	No indirectness
Interventions	(n=634) Intervention 1: Antiplatelet - Prasugrel. 60mg loading dose of prasugrel and 10mg once daily as a maintenance dose. In patients aged >75 years of age or in those with a weight <60kg, the maintenance dose of prasugrel was reduced to 5mg once daily. Administration of the loading dose was recommended immediately after the patients signed the informed consent. In individual cases in which the physician could not exclude the need for urgent surgical revascularisation on the basis of previous assessments or in cases involving haemodynamic instability, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI. In cases in which primary PCI was not performed, prasugrel therapy was discontinued and replaced by clopidogrel. The decision to perform the procedure was left to the discretion of the treating physician. Patients were advised to use the study medication for 12 months. Use of aspirin was also required with a recommendation of 100mg daily. Duration 30 days. Concurrent medication/care: The decision to administer any adjunctive medication to support PCI was left to the discretion of the treating physician. Indirectness: No indirectness

Study	PRAGUE-18 trial: Motovska 2016[119]
	Further details: 1. Timing of administration: Not applicable (n=596) Intervention 2: Antiplatelet - Ticagrelor. 180mg loading dose of ticagrelor and 90mg twice daily as a maintenance dose. Administration of the loading dose was recommended immediately after the patients signed the informed consent. In individual cases in which the physician could not exclude the need for urgent surgical revascularisation on the basis of previous assessments or in cases involving haemodynamic instability, antiplatelet therapy was delayed until after coronary angiography and immediately before or shortly after PCI. The decision to perform the procedure was left to the discretion of the treating physician. Patients were advised to use the study medication for 12 months. Use of aspirin was also required with a recommendation of 100mg daily. Duration 30 days. Concurrent medication/care: The decision to administer any adjunctive medication to support PCI was left to the discretion of the treating physician. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (Study funding not reported. Authors disclosed receiving speaking and advisory board fees and honoraria from industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus TICAGRELOR

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome: All-cause mortality at 30 days; Group 1: 14/634, Group 2: 16/596; Comments: Odds ratio: 0.82 (0.40-1.69)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality at 30 days
- Actual outcome: Cardiac mortality (death resulting from cardiovascular causes) at 30 days; Group 1: 8/634, Group 2: 8/596; Comments: Odds ratio: 0.94 (0.35-2.52)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)

- Actual outcome: Complications related to bleeding (BARC 3) at 30 days; Group 1: 4/634, Group 2: 2/596; Comments: Odds ratio: 1.60 (0.29-8.81)
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study	PRAGUE-18 trial: Motovska 2016[119]
Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (BARC 5) at 30 days; Group 1: 0/634, Group 2: 0/596 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (BARC 1) at 30 days; Group 1: 14/634, Group 2: 12/596; Comments: Odds ratio: 0.94 (0.43-2.05) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (BARC 2) at 30 days; Group 1: 10/634, Group 2: 10/596; Comments: Odds ratio: 0.81 (0.33-1.97) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Stroke - Actual outcome: Stroke (any, type not specified) at 30 days; Group 1: 2/634, Group 2: 1/596; Comments: Odds ratio: 1.88 (0.17-20.74) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Early and late stent thrombosis - Actual outcome: Stent thrombosis (definite) at 30 days; Group 1: 3/634, Group 2: 5/596; Comments: Odds ratio: 0.56 (0.13-2.35) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Re-infarction at 30 days - Actual outcome: Re-infarction at 30 days; Group 1: 8/634, Group 2: 7/596; Comments: Odds ratio: 1.07 (0.39-2.97) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics were balanced between the study groups' although more of the prasugrel group had a BMI ≥30 kg/m2 (P value 0.082); Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Quality of life; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	RAPID trial: Parodi 2013[185]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Italy; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: In-hospital follow up
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	STEMI: Patients with STEMI undergoing PPCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of STEMI within 21 hours of symptoms onset and informed consent
Exclusion criteria	Age <18 years; active bleeding or bleeding diathesis; any previous transient ischaemic attack/stroke; administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor; known relevant haematological deviations; life expectancy <1 year; or known severe liver or renal disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Prasugrel group: 67 (14 years); ticagrelor group: 67 (10 years). Gender (M:F): 39/11. Ethnicity: Not reported
Further population details	
Extra comments	Patients were randomised to study treatment before PPCI
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Antiplatelet - Prasugrel. A 60mg loading dose of prasugrel before PPCI. The loading dose was performed as soon as possible in the Emergency Room or in the Cath Lab. Dual antiplatelet therapy (100mg aspirin associated with 5 or 10mg prasugrel) was recommended for 12 months, with a loading dose of 500mg of aspirin followed by 100mg daily dose. Duration Unclear. Concurrent medication/care: Bivalirudin: bolus 0.75mg/kg followed by 1.75mg/kg/h infusion during PCI, after PPCI a bivalirudin infusion of 0.25mg/kg/h for 4 hours was allowed; unfractionated heparin use was discouraged; and glycoprotein IIb/IIIa inhibitors were not allowed. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=25) Intervention 2: Antiplatelet - Ticagrelor. A 180mg loading dose of ticagrelor before PPCI. The loading dose was performed as soon as possible in the Emergency Room or in the Cath Lab. Dual antiplatelet therapy (100mg aspirin associated with 180mg prasugrel) was recommended for 12 months, with a loading

Study	RAPID trial: Parodi 2013[185]
	dose of 500mg of aspirin followed by 100mg daily dose. Duration Unclear. Concurrent medication/care: Bivalirudin: bolus 0.75mg/kg followed by 1.75mg/kg/h infusion during PCI, after PPCI a bivalirudin infusion of 0.25mg/kg/h for 4 hours was allowed; unfractionated heparin use was discouraged; and glycoprotein IIb/IIIa inhibitors were not allowed. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (This study was supported by the "A.R. CARD" Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus TICAGRELOR

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: All-cause mortality (death) in-hospital (at 30 days); Group 1: 0/25, Group 2: 2/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Other adverse effects of treatment
- Actual outcome for STEMI: Other adverse effects (contrast-induced nephropathy) in-hospital (at 30 days); Group 1: 0/25, Group 2: 5/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Breathing adverse effects
- Actual outcome for STEMI: Breathing adverse effects (dyspnoea) in-hospital (at 30 days); Group 1: 0/25, Group 2: 5/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipdaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding (including haemorhragic stroke)
- Actual outcome for STEMI: Complications related to bleeding (major, TIMI) in-hospital (at 30 days); Group 1: 0/25, Group 2: 0/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes;

Study	RAPID trial: Parodi 2013[185]
Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: Complications related to bleeding (minor, TIMI) in-hospital (at 30 days); Group 1: 0/25, Group 2: 3/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis in-hospital (at 30 days); Group 1: 1/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction (myocardial infarction) in-hospital (at 30 days); Group 1: 1/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched' although at least twice as many of the ticagrelor group were affected by dyslipidaemia, previous MI and previous PCI compared with the prasugrel group, and twice as many of the prasugel group had diabetes; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Stroke; Need for revascularisation at 1 year; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Cardiac mortality at 30 days

Study	RAPID II trial: Parodi 2014[184]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Italy; Setting: Emergency department (with prior administration of aspirin in ambulance or at patient's home)
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 hours follow-up

Study	RAPID II trial: Parodi 2014[184]
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	STEMI: Undergoing primary PCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of STEMI within 12 hours of symptoms onset and informed written consent
Exclusion criteria	Age <18 years; active bleeding or bleeding diathesis; any previous transient ischaemic attack/stroke; administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor, or warfarin; known relevant haematological deviations; life expectancy of <1 year, and known severe liver or renal disease
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Prasugrel group: 67 (12 years); Ticagrelor group: 63 (11 years). Gender (M:F): 32/18. Ethnicity: Not reported
Further population details	
Extra comments	Patients pretreated by intravenous aspirin were randomised to treatment groups before PPCI. The loading dose was given as soon as possible in the emergency department or in the catheterisation laboratory
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Antiplatelet - Prasugrel. A loading dose of 500mg intravenous aspirin was administered in the ambulance or at the patient's home followed by 100mg daily dose. A 60mg loading dose of prasugrel was given before PPCI. The loading dose of prasugrel was performed as soon as possible in the emergency department or in the catheterisation laboratory. Dual antiplatelet therapy (100mg aspirin associated with 5 or 10mg prasugrel) was recommended for 12 months. Duration 12 hours. Concurrent medication/care: Bivalirudin: bolus of 0.75mg/kg followed by 1.75mg (kg h) infusion during PPCI. After PPCI, a bivalirudin infusion of 0.25mg (kg h) for 4 hours was performed in all the patients. Unfractionated heparin use was discouraged. Glycoprotein IIb/IIIa inhibitors were not allowed. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=25) Intervention 2: Antiplatelet - Ticagrelor. A loading dose of 500mg intravenous aspirin was administered in the ambulance or at the patient's home followed by 100mg daily dose. A 360mg loading dose of ticagrelor was given before PPCI. The loading dose of ticagrelor was performed as soon as possible in the emergency department or in the catheterisation laboratory. Dual antiplatelet therapy (100mg aspirin associated with 180mg ticagrelor) was recommended for 12 months. Duration 12 hours. Concurrent medication/care: Bivalirudin: bolus of 0.75mg/kg followed by 1.75mg (kg h) infusion during PPCI. After PPCI, a bivalirudin infusion of 0.25mg (kg h) for 4 hours was performed in all the patients. Unfractionated heparin use was discouraged. Glycoprotein IIb/IIIa inhibitors were not allowed. Indirectness: No indirectness

Study	RAPID II trial: Parodi 2014[184]
	Further details: 1. Timing of administration: Not applicable
Funding	Other (Study funding not reported. Authors disclosed receiving consulting or lecture fees and research grant funding from industry)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus TICAGRELOR

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: All-cause mortality (death) at 12 hours (at 30 days); Group 1: 1/25, Group 2: 1/25; Comments: Death due to cardiac tamponade in the prasugrel group and due to refractory heart failure in the ticagrelor group
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Bradycardic adverse effects
- Actual outcome for STEMI: Bradycardic adverse effects (ventricular pauses >3 seconds) at 12 hours (at 30 days); Group 1: 0/25, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Other adverse effects of treatment at 30 days
- Actual outcome for STEMI: Other adverse effects (contrast-induced nephropathy) at 12 hours (at 30 days); Group 1: 4/25, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome for STEMI: Complications related to bleeding (major, TIMI) at 12 hours (at 30 days); Group 1: 2/25, Group 2: 1/25
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: Complications related to bleeding (minor, TIMI) at 12 hours (at 30 days); Group 1: 0/25, Group 2: 2/25

Study	RAPID II trial: Parodi 2014[184]
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Stroke - Actual outcome for STEMI: Stroke (any, type not specified) at 12 hours (at 30 days); Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis (acute) at 12 hours (at 30 days); Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction at 12 hours (at 30 days); Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The 2 groups were well matched in all baseline characteristics, but there was a higher previous PCI rate in the ticagrelor group'. There was also a higher proportion of smokers in the ticagrelor group than in the prasugrel group; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; Cardiac mortality at 30 days

Study	Savonitto 2018[221]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1455)

Study	Savonitto 2018[221]
Countries and setting	Conducted in Italy; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months but premature discontinuation of study (3-12 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ST-segment elevation or NSTE-ACS had to show at least 1 of the following characteristics: elevated troponin levels, diabetes mellitus, prior myocardial infarction, ≥1 new ischaemic episode while on standard treatment during the index hospitalisation, or stent thrombosis
Stratum	Overall: Undergoing early percutaneous revascularisation
Subgroup analysis within study	Unclear: Subgroup analyses were conducted for the composite of all-cause mortality, myocardial infarction, disabling stroke, and rehospitalisation for cardiovascular causes or bleeding within 1 year. Treatment assignment was stratified by centre and type of ACS (STE versus NSTE)
Inclusion criteria	Patients >74 years of age with ST-segment elevation or NSTE-ACS treated with PCI during the index admission. Patients with NSTE-ACS had to show at least 1 of the following characteristics: elevated troponin levels, diabetes mellitus, prior myocardial infarction, ≥1 new ischaemic episode while on standard treatment during the index hospitalisation, or stent thrombosis
Exclusion criteria	Patients with a history of stroke, gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks, haemoglobin level on admission <10g/dL unless this was considered to be secondary to renal dysfunction or known myelodysplasia, platelet count <90,000 cells/mL, secondary causes of ischaemia, ongoing oral anticoagulant treatment or a spontaneous international normalised ratio >1.5 at the time of screening, concomitant severe obstructive lung disease, malignancy, or neurological deficit limiting follow-up or adherence to the study protocol. Patients unable to give at least verbal informed consent to the study or already under treatment with prasugrel or ticagrelor were also excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): 80 (77-84 years). Gender (M:F): 867/576. Ethnicity: Not reported
Further population details	
Extra comments	In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI (eg. on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomisation was to take place after angiography, and the loading dose should be administered either immediately before PCI or on arrival in the coronary care unit
Indirectness of population	No indirectness

Study	Savonitto 2018[221]
Interventions	(n=720) Intervention 1: Antiplatelet - Prasugrel. 60mg loading dose of prasugrel followed by 5mg once daily. In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI (eg. on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomisation was to take place after angiography, and the loading dose should be administered either immediately before PCI or on arrival in the coronary care unit. Ongoing clopidogrel treatment, either preexisting or started as soon as the diagnosis of NSTE-ACS was made (with a loading dose of 300 or 600mg left to the investigators' discretion), did not preclude enrollment. In this case, those randomised to prasugrel received a 30mg loading dose immediately after randomisation. All patients were to receive 325mg aspirin on admission and then 75 to 100mg daily throughout follow-up. Duration 12 months. Concurrent medication/care: Proton pump inhibitors were recommended in all patients throughout the study. The selection of periprocedural anticoagulants and glycoprotein IIb/IIIa receptor blockers was left to the investigators' discretion. Whereas the use of oral anticoagulants at the time of the index event was a contraindication to enrollment in the study, their subsequent use for conditions that could have developed during follow-up (eg. atrial fibrillation) was left to the discretion of the attending physician as clinically indicated. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=735) Intervention 2: Antiplatelet - Clopidogrel. 300-600mg loading dose of clopidogrel (at investigators' discretion) followed by 75mg once daily. In patients with STEMI undergoing primary PCI, the drugs could be given as soon as possible after the diagnosis, yet the first administration of the study drug could also take place after angiography or soon after PCI ((eg. on arrival in the coronary care unit), particularly in patients treated during PCI with glycoprotein IIb/IIIa receptor blockers. For patients treated with bivalirudin monotherapy during PCI, it was strongly recommended that the loading dose of the investigational drugs be administered before PCI. In patients with NSTE-ACS, randomisation was to take place after angiography, and the loading dose should be administered either immediately before PCI or on arrival in the coronary care unit. Ongoing clopidogrel treatment, either preexisting or started as soon as the diagnosis of NSTE-ACS was made (with a loading dose of 300 or 600mg left to the investigators' discretion), did not preclude enrollment. In this case, those randomised to clopidogrel were to continue clopidogrel 75mg daily without a further loading dose. All patients were to receive 325mg aspirin on admission and then 75 to 100mg daily throughout follow-up. Duration 12 months. Concurrent medication/care: Proton pump inhibitors were recommended in all patients throughout the study. The selection of periprocedural anticoagulants and glycoprotein IIb/IIIa receptor blockers was left to the investigators' discretion. Whereas the use of oral anticoagulants at the time of the index event was a contraindication to enrollment in the study, their subsequent use for conditions that could have developed during follow-up (eg. atrial fibrillation) was left to

Study	Savonitto 2018[221]
	the discretion of the attending physician as clinically indicated. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (The study has been promoted, managed and co-ordinated by Instituto di Ricerca e Cura a Carattere Scientfico Arcispedale Santa Maria Nuova in Reggio Emilia, Italy, and cofinanced by the pharmaceutical industry (Eli Lilly and Daiichi Sankyo))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL

Protocol outcome 1: Other adverse effects of treatment
- Actual outcome: Other adverse effects (premature study discontinuation due to adverse events) at 1 year; Group 1: 77/713, Group 2: 44/730
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Cardiac mortality
- Actual outcome: Cardiac mortality (cardiovascular death) at 1 year; Group 1: 26/713, Group 2: 31/730; Comments: Hazard ratio: 0.85 (0.51-1.4)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome: Complications related to bleeding (major, BARC 3) at 1 year; Group 1: 12/713, Group 2: 12/730
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Complications related to bleeding (major, BARC 5) at 1 year; Group 1: 1/713, Group 2: 0/730
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing:

Study	Savonitto 2018[221]
	- Actual outcome: Complications related to bleeding (minor, BARC 2) at 1 year; Group 1: 16/713, Group 2: 8/730 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (blood transfusion, 12 red blood cell units) at 1 year; Group 1: 12/713, Group 2: 9/735 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Stroke - Actual outcome: Stroke (any, type not specified) at 1 year; Group 1: 7/713, Group 2: 13/730; Comments: Hazard ratio: 0.55 (0.22-1.37) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Early and late stent thrombosis - Actual outcome: Stent thrombosis (probable or definite, acute) at 1 year; Group 1: 1/713, Group 2: 1/730 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Stent thrombosis (probable or definite, subacute) at 1 year; Group 1: 4/713, Group 2: 12/730 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Stent thrombosis (probable or definite, late) at 1 year; Group 1: 0/713, Group 2: 1/730 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well

Study	Savonitto 2018[221]
matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: All-cause mortality - Actual outcome: All-cause mortality at 1 year; Group 1: 36/713, Group 2: 28/730 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Re-infarction - Actual outcome: Re-infarction (myocardial infarction) at 1 year; Group 1: 14/713, Group 2: 19/730 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Unplanned urgent readmission - Actual outcome: Unplanned urgent readmission (rehospitalisation for cardiovascular causes) at 1 year; Group 1: 55/713, Group 2: 57/730 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Unplanned urgent readmission (rehospitalisation for bleeding) at 1 year; Group 1: 15/713, Group 2: 11/730 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - High; Indirectness of outcome: No indirectness ; Baseline details: 'baseline clinical and angiographic characteristics were well matched between groups, as were the coronary intervention procedures'; Blinding details: 'open-label, blinded end point trial...Study investigators and patients were not masked to treatment allocation...Study unblinding took place after the last patient had completed the 3-month follow-up'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; Re-infarction at 30 days; Length of hospital stay; All-cause mortality at up to 30 days

Study	Tang 2016[263]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=420)
Countries and setting	Conducted in China; Setting: All patients were hospitalised in the cardiac intensive care unit. During the 6-month follow-up, the data were recorded via telephone interviews or outpatient follow-up visits
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: ST segment elevation of >1mm in 2 or more limb leads or >2mm in 2 or more contiguous precordial leads
Stratum	STEMI: Undergoing PPCI
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years old; chest discomfort for >20 minutes and no response to nitroglycerin; time from the onset of symptoms to randomisation <12 hours; eligible for PPCI; ST segment elevation of >1mm in 2 or more limb leads or >2mm in 2 or more contiguous precordial leads; Killip class of ≤3; provision of informed consent
Exclusion criteria	Cardiogenic shock, defined as systolic blood pressure of <90/60mm Hg and no response to fluids; thrombolysis within the past 24 hours; oral anticoagulation therapy or current use of P2Y12 antagonists; malignant or life-threatening diseases; contraindications to aspirin, clopidogrel, or ticagrelor; inability to provide informed consent; suspected mechanical complications of STEMI; or coronary artery bypass graft surgery (CABG) within the previous year. Following angiography, patients were excluded if their angiographic findings included any of the following: stent thrombosis; multivessel disease requiring revascularisation or CABG; or no coronary vascular lesions
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 64.36 (11.409); Clopidogrel group: 64.18 (11.088). Gender (M:F): 288/112. Ethnicity: Not reported
Further population details	
Extra comments	Patients were randomised to treatment groups and received a loading dose before PPCI. The patients underwent angiography with or without stenting in accordance with practice guidelines
Indirectness of population	No indirectness
Interventions	(n=210) Intervention 1: Antiplatelet - Ticagrelor. Patients received 300mg of aspirin and a loading dose of 180mg ticagrelor before PPCI. After PPCI, the patients were given 100mg of aspirin daily and 90mg of ticagrelor twice daily. Duration 6 months. Concurrent medication/care: All patients without any contraindication also received conventional drugs, such as β-blockers, angiotensin-converting

Study	Tang 2016[263]
	enzymes/angiotensin receptor blockers, and statins in accordance with the 2013 ACCF/AHA guideline for the management of STEMI: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Some patients were treated with GPIIb/IIIa inhibitors [intracoronary bolus of tirofiban (10μg/kg) plus maintenance infusion (0.15μg-1.kg-1.min-1) for 24-36 hours] in accordance with the 2014 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation. The doctors who performed coronary angiography decided whether clopidogrel or ticagrelor treatments were supplemented with GPIIb/IIIa inhibitors after coronary angiography, but the doctors were blinded regarding the groups to which the patients belonged. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=210) Intervention 2: Antiplatelet - Clopidogrel. Patients received 300mg of aspirin and a loading dose of 600mg of clopidogrel before PPCI. After PPCI, the patients were given 100mg of aspirin daily and 75mg of clopidogrel once daily. Duration 6 months. Concurrent medication/care: All patients without any contraindication also received conventional drugs, such as β-blockers, angiotensin-converting enzymes/angiotensin receptor blockers, and statins in accordance with the 2013 ACCF/AHA guideline for the management of STEMI: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Some patients were treated with GPIIb/IIIa inhibitors [intracoronary bolus of tirofiban (10μg/kg) plus maintenance infusion (0.15μg-1.kg-1.min-1) for 24-36 hours] in accordance with the 2014 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularisation. The doctors who performed coronary angiography decided whether clopidogrel or ticagrelor treatments were supplemented with GPIIb/IIIa inhibitors after coronary angiography, but the doctors were blinded regarding the groups to which the patients belonged. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: Cardiac mortality
- Actual outcome for STEMI: Cardiac mortality (cardiovascular cause) at 6 months (at 1 year); Group 1: 3/200, Group 2: 5/200
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring

Study	Tang 2016[263]
CABG; 1 patient with no coronary vascular lesions Protocol outcome 2: Complications related to bleeding (including haemorrhagic stroke) - Actual outcome for STEMI: Complications related to bleeding (major, TIMI criteria) at (at 1 year); Group 1: 0/200, Group 2: 2/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions - Actual outcome for STEMI: Complications related to bleeding (minor, TIMI criteria) at 6 months (at 1 year); Group 1: 10/200, Group 2: 5/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions Protocol outcome 3: Stroke at Define - Actual outcome for STEMI: Stroke (any, type not specified) at 6 months (at 1 year); Group 1: 1/200, Group 2: 5/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions Protocol outcome 4: Need for revascularisation at 1 year - Actual outcome for STEMI: Need for revascularisation (unplanned revascularisation) at 6 months (at 1 year); Group 1: 0/200, Group 2: 3/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions Protocol outcome 5: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis at 6 months (at 1 year); Group 1: 0/200, Group 2: 3/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular	

Study	Tang 2016[263]
lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions Protocol outcome 6: All-cause mortality at 1 year - Actual outcome for STEMI: All-cause mortality at 6 months (at 1 year); Group 1: 4/200, Group 2: 6/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions Protocol outcome 7: Re-infarction at 1 year - Actual outcome for STEMI: Re-infarction (non-fatal myocardial infarction) at 6 months (at 1 year); Group 1: 0/200, Group 2: 3/200 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Both groups were similar in terms of baseline characteristics'; Group 1 Number missing: 10, Reason: 2 patients with stent thrombosis; 5 patients with multi-vessel disease requiring CABG; 2 patients with no coronary vascular lesions; 1 patient lost to follow-up; Group 2 Number missing: 10, Reason: 2 patients with stent thrombosis; 7 patients with multi-vessel disease requiring CABG; 1 patient with no coronary vascular lesions	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at up to 30 days ; Re-infarction at 30 days; Length of hospital stay at Define; Unplanned urgent readmission at within 30 days for any reason; All-cause mortality at up to 30 days

Study (subsidiary papers)	TRILOGY trial: Roe 2012[203] (Kaul 2016[69])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=9326)
Countries and setting	Conducted in Multiple countries; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: Study treatments continued for a minimum of 6 months and a maximum of 30 months - the median duration of exposure to a study drug was 14.8 months (interquartile range, 8.2 to 23.6 months)

Study (subsidiary papers)	TRILOGY trial: Roe 2012[203] (Kaul 2016[69])
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients with myocardial infarction without ST-segment elevation had elevated cardiac markers, whereas patients with unstable angina with negative cardiac markers had an ST-segment depression of more than 1mm in two or more electrocardiographic leads
Stratum	UA/NSTEMI: Not undergoing revascularisation
Subgroup analysis within study	Unclear: Prespecified subgroup analyses were performed for the primary efficacy endpoint, which was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients under the age of 75 years
Inclusion criteria	Patients with acute coronary syndromes were eligible if they were selected for a final treatment strategy of medical management without revascularisation within 10 days after the index event. Patients with myocardial infarction without ST segment elevation had elevated cardiac markers, whereas patients with unstable angina with negative cardiac markers had an ST segment depression of more than 1mm in two or more electrocardiographic leads. Patients were required to have at least one of four risk criteria: an age of at least 60 years, the presence of diabetes mellitus, previous myocardial infarction, or previous revascularisation with either PCI or coronary artery bypass grafting (CABG). Angiography was not required for enrollment, but if such a procedure was planned, it had to be performed before randomisation. Patients who underwent angiography were required to have evidence of coronary disease (native coronary stenosis of >30% or previous PCI or CABG)
Exclusion criteria	Major exclusion criteria included a history of transient ischaemic attack or stroke, PCI or CABG within the previous 30 days, renal failure requiring dialysis, and concomitant treatment with an oral anticoagulant
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): Prasugrel group: 66 (58-74 years); Clopidogrel group: 66 (59-73 years). Gender (M:F): Prasugrel group: 2835/1828; clopidogrel group: 2840/1823. Ethnicity: Not reported
Further population details	
Extra comments	Angiography was not a requirement for enrollment, but if such as procedure was planned, it had to be performed before randomisation. Patients who underwent randomisation within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of the study drug followed by a maintenance dose. Patients who did not undergo randomisation within 72 hours were required to be treated with open-label clopidogrel before randomisation and started on a maintenance dose of the study drug after randomisation
Indirectness of population	No indirectness
Interventions	(n=4663) Intervention 1: Antiplatelet - Prasugrel. Patients who underwent randomisation within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30mg of prasugrel, which was followed by daily blinded maintenance administration of a study drug. Patients who did not undergo randomisation within 72 hours were required to be treated with open-label clopidogrel before

Study (subsidiary papers)	TRILOGY trial: Roe 2012[203] (Kaul 2016[69])
	randomisation and were started on daily maintenance administration of a study drug after randomisation. The prasugrel maintenance dose was 10mg, which was adjusted to 5mg for patients who were 75 years of age or older or who weighed less than 60kg. Concomitant treatment with aspirin was required, and a daily dose of 100mg or less was strongly recommended. Duration 30 months. Concurrent medication/care: Not reported in study methods but the majority of patients received concomitant beta-blocker, ACE inhibitor or angiotensin-receptor blocker and statin at randomisation. Angiography was performed before randomisation in 41.2% of the prasugrel group. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=4663) Intervention 2: Antiplatelet - Clopidogrel. Patients who underwent randomisation within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 300mg of clopidogrel, which was followed by daily blinded maintenance administration of a study drug. Patients who did not undergo randomisation within 72 hours were required to be treated with open-label clopidogrel before randomisation and were started on daily maintenance administration of a study drug after randomisation. The clopidogrel maintenance dose was 75mg for all patients. Concomitant treatment with aspirin was required, and a daily dose of 100mg or less was strongly recommended. Duration 30 months. Concurrent medication/care: Not reported in study methods but the majority of patients received concomitant beta-blocker, ACE inhibitor or angiotensin-receptor blocker and statin at randomisation. Angiography was performed before randomisation in 41.4% of the clopidogrel group. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Other (Sponsor - Eli Lilly and Daiichi Sankyo)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL Protocol outcome 1: Quality of life - Actual outcome for UA/NSTEMI: Health-related quality of life (in patients aged <75 years, EQ-5D) at 1 year; Group 1: mean 85.6 (SD 15); n=2888, Group 2: mean 84.6 (SD 15.3); n=2876; EuroQol group 5-dimension (EQ-5D) descriptive system 'For each dimension, responders are asked to report their status on a 3-level ordinal scale: no problems (level 1), some problems (level 2), or severe problems (level 3)...The raw EQ-5D scores were multipled by 100 to make them more easily comaprable and to add more accuracy and discrimination between close scores with a decimal place' Top=Unclear; Comments: Baseline prasugrel group: 81.3 (16.8); baseline clopidogrel group: 80.8 (17.1) Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 1775; Group 2 Number missing: 1787 - Actual outcome for UA/NSTEMI: Health-related quality of life (in patients aged <75 years, SAQ Physical) at 1 year; Group 1: mean 78 (SD 23.4); n=891, Group 2: mean 77 (SD 23.2); n=883; Seattle Angina Questionnaire 0-100 Top=High is good outcome; Comments: Baseline prasugrel group: 71.9 (25.0);	

Study (subsidiary papers)	TRILOGY trial: Roe 2012[203] (Kaul 2016[69])

baseline clopidogrel group: 70.7 (25.6)
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 3772; Group 2 Number missing: 3780
- Actual outcome for UA/NSTEMI: Health-related quality of life (in patients aged <75 years, SF-12 Physical) at 1 year; Group 1: mean 44 (SD 10.7); n=891, Group 2: mean 43.7 (SD 10.7); n=883; Seattle Angina Questionnaire 0-100 Top=High is good outcome; Comments: Baseline prasugrel group: 41.3 (10.8); baseline clopidogrel group: 40.9 (11.1)
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 3772; Group 2 Number missing: 3780
- Actual outcome for UA/NSTEMI: Health-related quality of life (in patients aged <75 years, SF-12 Mental) at 1 year; Group 1: mean 49.7 (SD 10.5); n=891, Group 2: mean 49.7 (SD 10.3); n=883; Seattle Angina Questionnaire 0-100 Top=High is good outcome; Comments: Baseline prasugrel group: 48.3 (10.9); baseline clopidogrel group: 48.3 (11.5)
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 3772; Group 2 Number missing: 3780
- Actual outcome for UA/NSTEMI: Health-related quality of life (in patients aged <75 years, SF-36 Mental) at 1 year; Group 1: mean 48.2 (SD 11.3); n=891, Group 2: mean 47.8 (SD 11); n=883; Seattle Angina Questionnaire 0-100 Top=High is good outcome; Comments: Baseline prasugrel group: 45.9 (11.8); baseline clopidogrel group: 45.9 (12.1)
Risk of bias: All domain – Very High, Selection - Low, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 3772; Group 2 Number missing: 3780

Protocol outcome 2: All-cause mortality at 30 days
- Actual outcome: All-cause mortality at 30 days; Group 1: 39/4663, Group 2: 44/4663
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Cardiac mortality at 30 days
- Actual outcome for UA/NSTEMI: Cardiac mortality (death from cardiovascular causes) (in people aged <75 years) at 1 year; HR; 1.00 (95%CI 0.78 to 1.28);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome: Cardiac mortality (death from cardiovascular causes) at 30 days; Group 1: 35/4663, Group 2: 38/4663
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover

Study (subsidiary papers)	TRILOGY trial: Roe 2012[203] (Kaul 2016[69])
- Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Complications related to bleeding (including haemorragic stroke) at Define - Actual outcome: Major bleeding (TIMI Criteria) at 30 days; Group 1: 7/4663, Group 2: 6/4663 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Non-haemorrhagic stroke - Actual outcome for UA/NSTEMI: Stroke (any, type not specified) at 1 year; HR; 0.86 (95%CI 0.5 to 1.47); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Stroke at 30 days; Group 1: 12/4663, Group 2: 11/4663 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Re-infarction at 30 days - Actual outcome: Re-infarction at 30 days; Group 1: 74/4663, Group 2: 78/4663 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: Re-infarction at 1 year - Actual outcome for UA/NSTEMI: Re-infarction (all myocardial infarctions) at 1 year; HR; 0.97 (95%CI 0.78 to 1.19); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were generally well balanced in the two study groups' ; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcomes not reported by the study	Need for revascularisation at 1 year; Early and late stent thrombosis; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42,237])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=13,608)
Countries and setting	Conducted in Multiple countries; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 to 15 months follow up
Method of assessment of guideline condition	Partially adequate method of assessment/diagnosis: The inclusion criteria for patients with unstable angina or non-ST-elevation myocardial infarction were ischaemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomisation, a TIMI risk score of 3 or more, and either ST-segment deviation of 1mm or more or elevated levels of a cardiac biomarker of necrosis
Stratum	Overall: ACS undergoing PCI
Subgroup analysis within study	Not stratified but pre-specified: For composite outcome measures: UA/NSTEMI and STEMI; gender; age; diabetes; stent type; use of glycoprotein IIb/IIIa receptor-antagonist; creatinine clearance. Post-hoc subgroup analyses also included history or no history of stroke or TIA; age ≥75 years, body weight <60kg, or history of stroke or TIA, and age <75 years, body weight ≥60kg, and no history of stroke or TIA
Inclusion criteria	The inclusion criteria for patients with unstable angina or non-ST-elevation myocardial infarction were ischaemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomisation, a TIMI risk score of 3 or more, and either ST-segment deviation of 1mm or more or elevated levels of a cardiac biomarker of necrosis. Patients with ST-elevation myocardial infarction could be enrolled within 12 hours after the onset of symptoms if primary PCI was planned or within 14 days after receiving medical treatment for ST-elevation myocardial infarction
Exclusion criteria	Key exclusion criteria included an increased risk of bleeding, anaemia, thrombocytopaenia, a history of pathologic intracranial findings, or the use of any thienopyridine within 5 days before enrollment
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Prasugrel group median (25th percentile, 75th percentile): 61 (53-69 years); clopidogrel group median (25th percentile, 75th percentile): 61 (53-70 years). Gender (M:F): Prasugrel group: 5110/1703; clopidogrel group: 4960/1835. Ethnicity: Prasugrel group: white 92%, non-white 8%; clopidogrel group: white 93%, non-white 7 %
Further population details	
Extra comments	Randomisation was to occur before PCI was performed, and the study drug was to be administered as soon as possible after randomisation
Indirectness of population	No indirectness

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42,237])
Interventions	(n=6813) Intervention 1: Antiplatelet - Prasugrel. A loading dose of 60mg prasugrel was administered anytime between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. If the coronary anatomy was previously known or primary PCI for ST-elevation myocardial infarction was planned, pretreatment with the study drug was permitted for up to 24 hours before PCI. After PCI, patients received a maintenance dose of 10mg prasugrel daily. Use of aspirin was required, and a daily dose of 75 to 162mg was recommended. Duration 15 months. Concurrent medication/care: The choice of vessels treated, devices used, and adjunctive medication administered to support PCI was left to the discretion of the treating physician. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=6795) Intervention 2: Antiplatelet - Clopidogrel. A loading dose of 300mg clopidogrel was administered anytime between randomisation and 1 hour after leaving the cardiac catheterisation laboratory. If the coronary anatomy was previously known or primary PCI for ST-elevation myocardial infarction was planned, pretreatment with the study drug was permitted for up to 24 hours before PCI. After PCI, patients received a maintenance dose of 75mg clopidogrel daily. Use of aspirin was required, and a daily dose of 75 to 162mg was recommended. Duration 15 months. Concurrent medication/care: The choice of vessels treated, devices used, and adjunctive medication administered to support PCI was left to the discretion of the treating physician. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable
Funding	Study funded by industry (Supported by research grants from Daiichi Sankyo and Eli Lilly)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRASUGREL versus CLOPIDOGREL

<u>ACS (with/without revasuclarisation)</u>

Protocol outcome 1: All-cause mortality at 1 year
- Actual outcome: All-cause mortality (death from any cause) at 15 months; Group 1: 188/6813, Group 2: 197/6795; Comments: Hazard ratio for prasugrel (95% CI): 0.95 (0.78 to 1.16)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome: Complications related to bleeding (non-CABG-related major, TIMI) at 15 months; Group 1: 146/6741, Group 2: 111/6716; Comments: Hazard ratio for prasugrel (95% CI): 1.32 (1.03 to 1.68)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42,237])
Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (CABG-related major, TIMI) at 15 months; Group 1: 24/6741, Group 2: 6/6716; Comments: Hazard ratio for prasugrel (95% CI): 4.73 (1.90 to 11.82) Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (major or minor, TIMI) at 15 months; Group 1: 303/6741, Group 2: 231/6716; Comments: Hazard ratio for prasugrel (95% CI): 1.31 (1.11 to 1.56) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Other adverse effects of treatment - Actual outcome: Other adverse effects (severe thrombocytopaenia) at 15 months; Group 1: 17/6741, Group 2: 18/6716 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Other adverse effects (neutropenia) at 15 months; Group 1: 2/6741, Group 2: 10/6716 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Cardiac mortality - Actual outcome: Cardiac mortality (death from cardiovascular causes) at 15 months; Group 1: 133/6813, Group 2: 150/6795; Comments: Hazard ratio for prasugrel (95% CI): 0.89 (0.70 to 1.12) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Group 1 Number missing: ; Group 2 Number missing:	

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42 ,237])

Protocol outcome 5: Stroke
- Actual outcome: Stroke (any non-fatal, type not specified) at 15 months; Group 1: 61/6813, Group 2: 60/6795; Comments: Hazard ratio for prasugrel (95% CI): 1.02 (0.71 to 1.45)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Need for revascularisation at 1 year
- Actual outcome: Need for revascularisation (urgent target vessel revascularisation) at 15 months; Group 1: 156/6813, Group 2: 233/6795; Comments: Hazard ratio for prasugrel (95% CI): 0.66 (0.56 to 0.81)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Early and late stent thrombosis
- Actual outcome: Stent thrombosis (definite or probable) at 15 months; Group 1: 68/6813, Group 2: 142/6795; Comments: Hazard ratio for prasugrel (95% CI): 0.48 (0.36 to 0.64)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The baseline characteristics were...well matched between groups' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:

<u>STEMI + revascularisation</u>

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: STEMI subgroup: all-cause mortality (death) at 30 days; Group 1: 28/1769, Group 2: 45/1765; Comments: Hazard ratio (95% CI): 0.62 (0.39-0.99)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42 ,237])

Protocol outcome 2: Need for revascularisation
- Actual outcome for STEMI: STEMI subgroup: Need for revascularisation (urgent target revascularisation) at 15 months; Group 1: 38/1769, Group 2: 54/1765; Comments: Hazard ratio (95% CI): 0.70 (0.46-1.06)
Risk of bias: All domain – Very High, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome for STEMI: STEMI subgroup: complications related to bleeding (major, TIMI) at 30 days; Group 1: 17/1769, Group 2: 23/1765; Comments: Number analysed using available case analysis. Hazard ratio (95% CI): 0.74 (0.39-1.38)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:
No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:
Protocol outcome 4: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome for STEMI: STEMI subgroup: complications related to bleeding (non-CABG related major, TIMI) at 15 months; Group 1: 38/1769, Group 2: 34/1765; Comments: Number analysed using available case analysis. Hazard ratio (95% CI): 1.11 (0.70-1.77)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STEMI subgroup: complications related to bleeding (minor, TIMI) at 30 days; Group 1: 35/1769, Group 2: 57/1765; Comments: Number analysed using available case analysis. Hazard ratio (95% CI): 0.91 (0.62-1.32)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Cardiac mortality
- Actual outcome for STEMI: STEMI subgroup: cardiac mortality (cardiovascular death) at 30 days; Group 1: 25/1769, Group 2: 41/1765; Comments: Hazard ratio (95% CI): 0.61 (0.37-1.00)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STEMI subgroup: cardiac mortality (cardiovascular death) at 15 months (1 year); Group 1: 43/1769, Group 2: 58/1765; Comments: Hazard ratio (95% CI): 0.74 (0.50-1.09)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42,237])
Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Need for revascularisation - Actual outcome for STEMI: STEMI subgroup: need for revascularisation (urgent target vessel revascularisation) at 30 days; Group 1: 22/1769, Group 2: 33/1765; Comments: Hazard ratio (95% CI): 0.66 (0.39-1.14) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Early and late stent thrombosis - Actual outcome for STEMI: STEMI subgroup: stent thrombosis at 30 days; Group 1: 19/1769, Group 2: 39/1765; Comments: Hazard ratio (95% CI): 0.49 (0.28-0.84) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: All-cause mortality at 1 year - Actual outcome for STEMI: STEMI subgroup: all-cause mortality (death) at 15 months; Group 1: 58/1769, Group 2: 76/1765; Comments: Hazard ratio (95% CI): 0.76 (0.54-1.07) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Re-infarction - Actual outcome for STEMI: STEMI subgroup: re-infarction (myocardial infarction) at 30 days; Group 1: 87/1769, Group 2: 123/1765; Comments: Hazard ratio (95% CI): 0.70 (0.53-0.92) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for STEMI: STEMI subgroup: re-infarction (myocardial infarction) at 15 months; Group 1: 119/1769, Group 2: 157/1765; Comments: Hazard ratio (95% CI): 0.75 (0.59-0.95) Risk of bias: All domain – Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:	

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42 ,237])

Protocol outcome 9: Stroke
- Actual outcome for STEMI: STEMI subgroup: stroke (any, type not specified) at 30 days; Group 1: 7/1769, Group 2: 16/1765; Comments: Hazard ratio (95% CI): 0.43 (0.18-1.06)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for STEMI: STEMI subgroup: stroke (any, type not specified) at 15 months; Group 1: 26/1769, Group 2: 25/1765; Comments: Hazard ratio (95% CI): 1.03 (0.60-1.79)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'Baseline characteristics were well matched'; Group 1 Number missing: ; Group 2 Number missing:

<u>UA/STEMI + revascularisation</u>

Protocol outcome 1: Stroke
- Actual outcome for UA/NSTEMI: NSTE-ACS subgroup: stroke (any, type not specified) at 15 months (1 year); Group 1: 49/5044, Group 2: 46/5030; Comments: Hazard ratio (95% CI): 1.07 (0.71-1.60)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Post-hoc analysis baseline details reported for subpopulation with NSTE-ACS: 'Overall, baseline characteristics were well matched' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Re-infarction
- Actual outcome for UA/NSTEMI: NSTE-ACS subgroup: re-infarction (all myocardial infarctions) at 15 months (1 year); Group 1: 366/5044, Group 2: 476/5030; Comments: Hazard ratio (95% CI): 0.76 (0.66-0.87)
Risk of bias: All domain - All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Post-hoc analysis baseline details reported for subpopulation with NSTE-ACS: 'Overall, baseline characteristics were well matched' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Cardiac mortality
- Actual outcome for UA/NSTEMI: NSTE-ACS subgroup: cardiac mortality (cardiovascular deaths) at 15 months (1 year); Group 1: 90/5044, Group 2: 92/5030; Comments: Hazard ratio (95% CI): 0.98 (0.73-1.31)
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study (subsidiary papers)	TRITON-TIMI 38 trial: Wiviott 2007[308] (Montalescot 2009[116], Servi 2014[42,237])
Indirectness of outcome: No indirectness ; Baseline details: Post-hoc analysis baseline details reported for subpopulation with NSTE-ACS: 'Overall, baseline characteristics were well matched' ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Complications relating to bleeding - Actual outcome for UA/NSTEMI: NSTE-ACS subgroup: complications related to bleeding (non-CABG related major, TIMI) at 15 months (1 year); Group 1: 108/5001, Group 2: 77/4980; Comments: Hazard ratio (95% CI): 1.40 (1.05-1.88) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Post-hoc analysis baseline details reported for subpopulation with NSTE-ACS: 'Overall, baseline characteristics were well matched' ; Blinding details: 'All components of the primary, secondary, and key safety end points were adjudicated by members of an independent clinical events committee that was unaware of the group assignments'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Length of hospital stay

Study	Wang 2016a[289]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of ACS made according to the European Society of Cardiology guideline
Stratum	Overall: The majority of the population underwent an invasive strategy during the study (PCI during study: 73%)
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of ACS made according to the European Society of Cardiology guideline
Exclusion criteria	Any contraindication against the use of P2Y12 inhibitors; under DAPT, anticoagulation, and fibrinolytic therapy; active bleeding or increased bleeding risk such as malignancy, surgery, trauma, fracture, or organ biopsy; clinically significant out-of-range values for platelet count or haemoglobin; had renal function failure

Study	Wang 2016a[289]
	requiring dialysis; hypertension with systolic blood pressure >180mmHg or diastolic blood pressure >110mmHg, or cardiogenic shock with systolic blood pressure <80mmHg lasting for >30 minutes
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): 79 (65-93 years). Gender (M:F): Clopidogrel group: 66/33; Ticagrelor group: 69/31. Ethnicity: Chinese
Further population details	
Extra comments	Patients older than 65 years were recruited. The initial loading dose of study drugs was administered as soon as possible after randomisation
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Antiplatelet - Clopidogrel. Clopidogrel was administered at a 300mg loading dose with a maintenance dose of 75mg once daily. The initial loading dose was administered as soon as possible after randomisation with the first maintenance dose administered at the usual time. All patients took aspirin at a loading dose of 300mg followed by a maintenance dose of 100mg once daily, unless aspirin was intolerant. Duration 12 months. Concurrent medication/care: not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable (n=100) Intervention 2: Antiplatelet - Ticagrelor. Ticagrelor was adminstered at 180mg loading dose, and then a maintenance dose of 90mg twice daily. The initial loading dose was administered as soon as possible after randomisation with the first maintenance dose administered at the usual time. All patients took aspirin at a loading dose of 300mg followed by a maintenance dose of 100mg once daily, unless aspirin was intolerant. Duration 12 months. Concurrent medication/care: not reported. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus TICAGRELOR

Protocol outcome 1: Complications related to bleeding (including haemorragic stroke)
- Actual outcome: Complications related to bleeding (major, PLATO) at 1 year; Group 1: 6/100, Group 2: 8/100; Comments: Hazard ratio: 1.250 (0.434-3.604)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing:

Study	Wang 2016a[289]
- Actual outcome: Complications related to bleeding (minor, PLATO) at 1 year; Group 1: 8/100, Group 2: 13/100; Comments: Hazard ratio: 1.531 (0.634-3.694) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Stroke - Actual outcome: Stroke (any, type not specified) at 1 year; Group 1: 3/100, Group 2: 2/100; Comments: Hazard ratio: 0.623 (0.104-3.732) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: All-cause mortality at 1 year - Actual outcome: All-cause mortality at 1 year; Group 1: 16/100, Group 2: 9/100; Comments: Hazard ratio: 0.534 (0.236-1.209) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Cardiac mortality (cardiovascular death) at 1 year; Group 1: 15/100, Group 2: 6/100; Comments: Hazard ratio: 0.381 (0.148-0.982) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Re-infarction at 1 year - Actual outcome: Re-infarction (myocardial infarction) at 1 year; Group 1: 15/100, Group 2: 6/100; Comments: Hazard ratio: 0.380 (0.148-0.981) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'baseline characteristics and clinical diagnosis had no significant difference between patients taking ticagrelor and clopidogrel; they were also balanced with respect to other treatments (P>0.05 for all); Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days ; Cardiac mortality at 30 days ; Need for revascularisation at 1 year; Early and late stent thrombosis; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Wang 2016b[290]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in China; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 30 days follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Acute myocardial infarction within 12 hours after onset of chest pain; and ECG indications of sustained elevation of 2 adjacent ST segments or newly emerging left bundle branch block
Stratum	STEMI: Undergoing emergency PCI
Subgroup analysis within study	Not applicable
Inclusion criteria	Age ≥60 years; dementia; acute myocardial infarction within 12 hours after onset of chest pain; and ECG indications of sustained elevation of 2 adjacent ST segments or newly emerging left bundle branch block
Exclusion criteria	Age ≥80 years; presence of chronic obstructive pulmonary disease at acute exacerbation stage, bronchial asthma, malignant tumour, or kidney failure, any contraindication of using clopidogrel, nearly onset cerebral infarction in the last year or previous history of cerebral haemorrhage; severe sinus bradycardia (heart rate <50 beats/min), cardiogenic shock, type II atrioventricular block above degree II, receiving intravenous thrombolysis within 24 hours, and currently receiving anticoagulant therapy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Range: 60-79 years. Gender (M:F): Ticagrelor group: 48/39; Clopidogrel group: 50/37. Ethnicity: Not reported
Further population details	
Extra comments	Patients were randomised into treatment groups. They received a loading dose of aspirin if they were no already taking aspirin. Immediately after the loading dose of aspirin, patients underwent coronary arteriography and PCI
Indirectness of population	No indirectness
Interventions	(n=87) Intervention 1: Antiplatelet - Ticagrelor. Loading dose of 180mg ticagrelor and then switched to an oral maintenance dose of 90mg twice daily. Duration 30 days. Concurrent medication/care: If patients were not already taking aspirin, they received aspirin at a loading dose of 300mg. After the loading dose of aspirin, patients immediately underwent coronary arteriography and PCI. Indirectness: No indirectness

Study	Wang 2016b[290]
	Further details: 1. Timing of administration: Not applicable (n=87) Intervention 2: Antiplatelet - Clopidogrel. Loading dose of 600mg clopidogrel and then switched to an oral maintenance dose of 75mg daily. Duration 30 days. Concurrent medication/care: If patients were not already taking aspirin, they received aspirin at a loading dose of 300mg. After the loading dose of aspirin, patients immediately underwent coronary arteriography and PCI. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR versus CLOPIDOGREL

Protocol outcome 1: Other adverse effects of treatment at up to 30 days
- Actual outcome for STEMI: Other adverse effects (upper gastrointestinal bleeding) at 30 days; Group 1: 4/87, Group 2: 2/87; Comments: Odds ratio: 2.41 (1.17-3.20)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Breathing adverse effects
- Actual outcome for STEMI: Breathing adverse effects (difficulty breathing) at 30 days; Group 1: 12/87, Group 2: 5/87; Comments: Odds ratio: 2.04 (1.08-2.98)
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Bradycardic adverse effects
- Actual outcome for STEMI: Bradycardic adverse effects (sinus bradycardia) at 30 days; Group 1: 7/87, Group 2: 4/87; Comments: Odds ratio: 1.18 (0.89-1.35)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing:

Study	Wang 2016b[290]
- Actual outcome for STEMI: Bradycardic adverse effects (required permanent pacemaker implantation) at 30 days; Group 1: 2/87, Group 2: 2/87 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Other adverse effects - Actual outcome for STEMI: Other adverse effects (malignant ventricular arrhythmias) at 30 days; Group 1: 5/87, Group 2: 6/87; Comments: Odds ratio: 0.98 (0.81-1.33) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Cardiac mortality at 30 days - Actual outcome for STEMI: Cardiac mortality (vascular causes of death) at 30 days; Group 1: 2/87, Group 2: 4/87; Comments: Odds ratio: 0.63 (0.34-0.89) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 6: Stroke - Actual outcome for STEMI: Stroke (any, type not specified) at 30 days; Group 1: 2/87, Group 2: 2/87 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 7: Early and late stent thrombosis - Actual outcome for STEMI: Stent thrombosis at 30 days; Group 1: 0/87, Group 2: 4/87 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 8: Re-infarction at 30 days

Study	Wang 2016b[290]
- Actual outcome for STEMI: Re-infarction (recurrent myocardial infarction) at 30 days; Group 1: 1/87, Group 2: 5/87; Comments: Odds ratio: 0.55 (0.12-0.79) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics similar for gender, cardiovascular risk factors, previous myocardial infarction, anterior and inferior wall infarction, troponin I-negative and I-positive, and STEMI risk factors. However, age data were not reported by intervention group ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Complications related to bleeding (including haemorrhagic stroke); Need for revascularisation at 1 year; All-cause mortality at 1 year; Length of hospital stay; Re-infarction at 1 year; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Wang 2019[291]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=298)
Countries and setting	Conducted in China; Setting:
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	STEMI
Subgroup analysis within study	Not applicable
Inclusion criteria	Acute myocardial ischemia lasting more than 30 minutes and ST-segment elevation of at least 0.1 mV in at least two extremity leads or at least 0.2 mV in at least two precordial leads detected on a 12-lead ECG, and the presence of symptoms for less than 12 hours.
Exclusion criteria	Cardiogenic shock, thrombolysis within the last 24 hours, oral anticoagulant therapy, indication for emergency coronary artery bypass grafting, known allergy to: aspirin, clopidogrel, ticagrelor, or heparin, active severe bleeding, pregnancy, severe uncontrolled hypertension, severe renal failure, inability to provide informed consent, and presenting with left bundle branch block.
Recruitment/selection of patients	Consecutive patients with STEMI eligible for primary PCI were enrolled form June 2015 to January 2017.

Study	Wang 2019[291]
Age, gender and ethnicity	Age - Mean (SD): ticagrelor group: 60 (13); clopidogrel group: 61 (12). Gender (M:F): 236/62. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=150) Intervention 1: Antiplatelet - Ticagrelor. Patients were administered a loading dose of ticagrelor, 180 mg followed by 90 mg twice daily.. Duration Not reported. Concurrent medication/care: Coronary angiography and PCI were performed according to standard protocols, loaded with heparin and then additional heparin was administered to maintain an activated clotting time of more than 300 seconds. Drug-eluting stents were used for all patients. . Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Routine (Administered at operator's discretion). (n=148) Intervention 2: Antiplatelet - Clopidogrel. Patients were administered clopidogrel loading dose of 600 mg, followed by 75 mg daily. . Duration Not reported. Concurrent medication/care: Coronary angiography and PCI were performed according to standard protocols, loaded with heparin and then additional heparin was administered to maintain an activated clotting time of more than 300 seconds. Drug-eluting stents were used for all patients. . Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Routine (Administered at operator's discretion).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR + ASA versus CLOPIDOGREL + ASA

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for STEMI: All-cause mortality at 30 days; Group 1: 3/150, Group 2: 6/148
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Complications related to bleeding (including haemorragic stroke)
- Actual outcome for STEMI: Major bleeding at During hospitalisation (at 30 days); Group 1: 5/150, Group 2: 4/148
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for STEMI: Minor bleeding at During hospitalisation (at 30 days); Group 1: 15/150, Group 2: 10/148
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Wang 2019[291]
Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Need for revascularisation at 1 year - Actual outcome for STEMI: Urgent TVR at up to 1 year (6 months); Group 1: 4/150, Group 2: 11/148 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for STEMI: Urgent TVR at 30 days; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: All-cause mortality at 1 year - Actual outcome for STEMI: All-cause mortality at up to 1 year (6 months); Group 1: 3/150, Group 2: 7/148 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Re-infarction at 30 days - Actual outcome for STEMI: Re-infarction at 30 days; Group 1: 3/150, Group 2: 7/148 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Re-infarction at 1 year - Actual outcome for STEMI: Re-infarction at up to 1 year (6 months); Group 1: 4/150, Group 2: 10/148 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cardiac mortality at 30 days ; Non-haemorrhagic stroke; Early and late stent thrombosis; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; Other adverse effects of treatment (eg. breathlessness, bradycardia) at 30 days

Study	Wu 2018[313]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=257)
Countries and setting	Conducted in China; Setting: Emergency Department of Hebei General Hospital
Line of therapy	Not applicable

Study	Wu 2018[313]
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	UA/NSTEMI
Subgroup analysis within study	Not applicable
Inclusion criteria	Non STEMI patients should meet at least two of the following criteria; (1) the electrocardiogram (ECG) presented with decreased ST segments in ≥0.1 mv of transient elevated ST segment; (2) assay results of the myocardial injury markers (such as Mb or CK-MB, or cTnI or cTnT) were positive; (3) patients presented with at least one of following risk factors: age ≥60 years olds, hyperlipidemia, hypertension, diabetes mellitus, history of myocardial infarction ≥50% vascular stenoses in ≥2 branches of the coronary artery, history of cerebral infarction, transient ischemic attack (TIA) diagnosed by the hospital, carotid canal presented with ≥50% stenosis, history of revascularisation of cerebral blood vessels, peripheral arterial disease, and chronic renal dysfunction. Additionally, STEMI patients should meet the following criteria: the ECG presented with elevated ST segments in ≥ 2 consecutive leads and ≥0.1 mv, or a left bundle branch block was newly detected.
Exclusion criteria	Not reported - as per the inclusion criteria
Recruitment/selection of patients	Consecutive patients treated with emergency PCI
Age, gender and ethnicity	Age - Mean (SD): Ticagrelor group: 59 (10); clopidogrel group: 61 (12). Gender (M:F): 192/52. Ethnicity: Not reported
Further population details	
Extra comments	Total study population: 232/244 (95%) - STEMI patients; 12/244 (5%) - NSTEMI patients
Indirectness of population	No indirectness
Interventions	(n=129) Intervention 1: Antiplatelet - Ticagrelor. Patients in orally took a loading dose of aspirin (300 mg). After diagnosis, patients in the ticagrelor group took 180 mg of ticagrelor (qd), and subsequently took 90 mg of ticagrelor (bid) for maintenance.. Duration Not reported. Concurrent medication/care: n/a. Indirectness: No indirectness Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear (n=128) Intervention 2: Antiplatelet - Clopidogrel. Patients in orally took a loading dose of aspirin (300 mg). After diagnosis, patients in the clopidogrel group took 300 mg of clopidogrel (qd), and subsequently took 75 mg of clopidogrel (bid) for maintenance.. Duration Not reported. Concurrent medication/care: n/a. Indirectness: No indirectness

Study	Wu 2018[313]
	Further details: 1. Timing of adminstration: Administration after hospital admission 2. Use of GpIIb/IIIa : Not stated / Unclear
Funding	Academic or government funding (Fund Project: The task book of Hebei Science and Technology Project)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TICAGRELOR + ASA versus CLOPIDOGREL + ASA

Protocol outcome 1: Other adverse effects of treatment (eg. breathlessness, bradycardia)
- Actual outcome for STEMI: Bradycardia at 1 year; Group 1: 1/124, Group 2: 0/120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up

Protocol outcome 2: Cardiac mortality
- Actual outcome for STEMI: Cardiac mortality (cardiovascular death) at 1 year; Group 1: 0/124, Group 2: 2/120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up

Protocol outcome 3: Complications related to bleeding (including haemorragic stroke)
- Actual outcome for STEMI: Bleeding event, type not specified (haemorrphagic event) at 1 year; Group 1: 14/124, Group 2: 4/120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up

Protocol outcome 4: Non-haemorrhagic stroke
- Actual outcome for STEMI: Stroke at 1 year; Group 1: 1/124, Group 2: 4/120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up

Protocol outcome 5: Early and late stent thrombosis
- Actual outcome for STEMI: Stent thrombosis at 1 year; Group 1: 0/124, Group 2: 0/120
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up

Study	Wu 2018[313]
Protocol outcome 6: Re-infarction at 1 year - Actual outcome for STEMI: Re-infarction (recurrent myocardial infarction) at 1 year; Group 1: 0/124, Group 2: 3/120 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: Lost to follow-up; Group 2 Number missing: 8, Reason: Lost to follow-up	
Protocol outcomes not reported by the study	Quality of life; Need for revascularisation at 1 year; All-cause mortality at 1 year; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Study	Yao 2017[321]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: In hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: six-month follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: 'diagnostic criteria of the guideline from American Heart Association for acute myocardial infarction published in 2000'
Stratum	Overall: Undergoing emergency PCI
Subgroup analysis within study	Not applicable:
Inclusion criteria	'diagnostic criteria of the guideline from American Heart Association for acute myocardial infarction published in 2000; patients who are younger than 75 years old; patients who had received emergency PCI and followed up according to medical order with complete clinical data; patients took neither anticoagulants like warfarin or others, nor antiplatelet medication like clopidogrel and ticagrelor within a week'
Exclusion criteria	'patients who had severe cardiogenic shock and cardiac insufficiency; patients who had [taken] anticoagulant like warfarin within a week; patients who were complicated other diseases such as severe coagulation disorders, moderate or severe anaemia, active peptic ulceration, intracerebral haemorrhage, therioma, etc.; patients who were allergic to aspirin, clopidogrel and ticagrelor'
Recruitment/selection of patients	Not reported

Study	Yao 2017[321]
Age, gender and ethnicity	Age - Other: 'average age of 60.2 ± 12.3' (clopidogrel group: 59.8 ± 10.8; ticagrelor group: 60.4 ± 12.7). Gender (M:F): 74/46 (clopidogrel group: 36/24; ticagrelor group: 38/22). Ethnicity: Not reported
Further population details	
Extra comments	Timing of randomisation to treatment unclear. Loading doses of study drugs were administered before emergency PCI
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Antiplatelet - Clopidogrel. Before the emergency PCI surgery, a loading dose of clopidogrel (Sanofi-Aventis Co. Ltd.) 600 mg and aspirin (Bayer AG) 300 mg were administered orally. Duration 6 months. Concurrent medication/care: All patients received basic treatment for AMI, including 'atorvastatin, isosorbide mononitrate, metroprolol and so forth every day. After PCI, they were all hypodermic injected with enoxaparin sodium (brand name: clexane, brought from Sanofi-Aventis Co. Ltd., licence number: H20100484 for anticoagulation'. Indirectness: No indirectness Further details: 1. Timing of adminstration: Not applicable (n=60) Intervention 2: Antiplatelet - Ticagrelor. Before the emergency PCI surgery, a loading dose of ticagrelor (AstreZeneca, AB) 180 mg and aspirin (Bayer, AG) 300 mg were administered orally. Duration 6 months. Concurrent medication/care: All patients received basic treatment for AMI, including 'atorvastatin, isosorbide mononitrate, metroprolol and so forth every day. After PCI, they were all hypodermic injected with enoxaparin sodium (brand name: clexane, brought from Sanofi-Aventis Co. Ltd., licence number: H20100484 for anticoagulation'. Indirectness: No indirectness Further details: 1. Timing of administration: Not applicable
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL versus TICAGRELOR

Protocol outcome 1: Other adverse effects of treatment
- Actual outcome: Other adverse effects (recurrent angina) at 6 months (at 1 year); Group 1: 8/60, Group 2: 5/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;
Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)';
Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Complications related to bleeding (including haemorrhagic stroke)
- Actual outcome: Complications related to bleeding (major, BARC 3-5) at 6 months (at 1 year); Group 1: 1/60, Group 2: 0/60
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low;

Study	Yao 2017[321]
Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)'; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Complications related to bleeding (minor, BARC 1-2) at 6 months (at 1 year); Group 1: 24/60, Group 2: 10/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Need for revascularisation at 1 year - Actual outcome: Need for revascularisation (second PCI) at 6 months; Group 1: 5/60, Group 2: 3/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: All-cause mortality at 1 year - Actual outcome: All-cause mortality at 6 months; Group 1: 1/60, Group 2: 0/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)'; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 5: Re-infarction at 1 year - Actual outcome: Re-infarction (second myocardial infarction) at 6 months; Group 1: 6/60, Group 2: 3/60 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low; Indirectness of outcome: No indirectness ; Baseline details: 'The age, sex, primary diseases and other parameters had no statistical difference (P>0.05)'; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Cardiac mortality at 30 days ; Stroke; Early and late stent thrombosis; Re-infarction at 30 days; Length of hospital stay; Unplanned urgent readmission within 30 days for any reason; All-cause mortality at 30 days

Appendix E: Forest plots

E.1 Ticagrelor + aspirin (ASA) versus clopidogrel + ASA

Figure 5: All-cause mortality at 30 days (ACS with/without revascularisation)

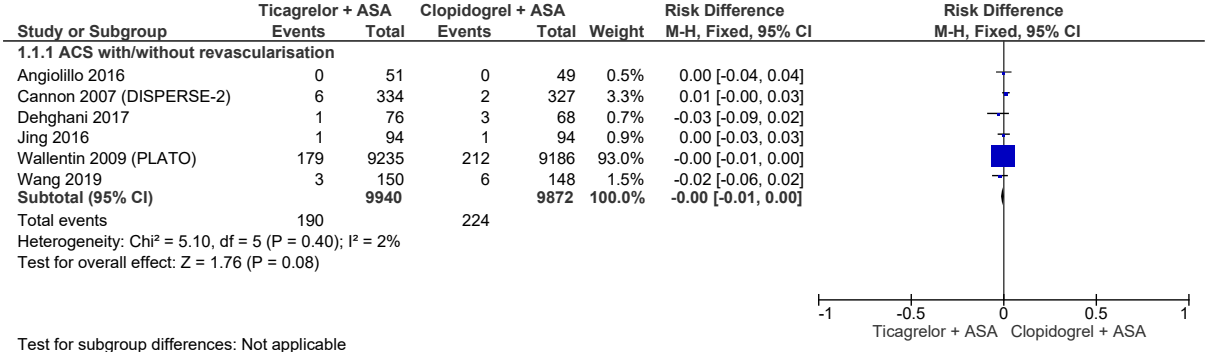


Figure 6: All-cause mortality at 30 days (STEMI + revascularisation)

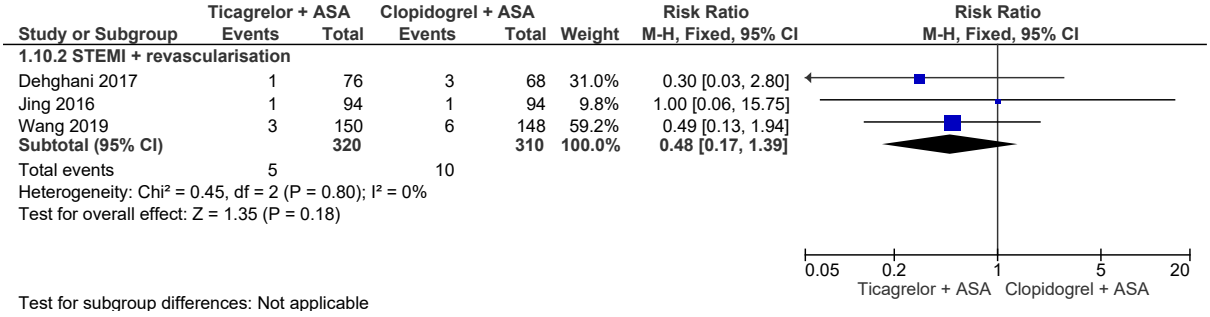
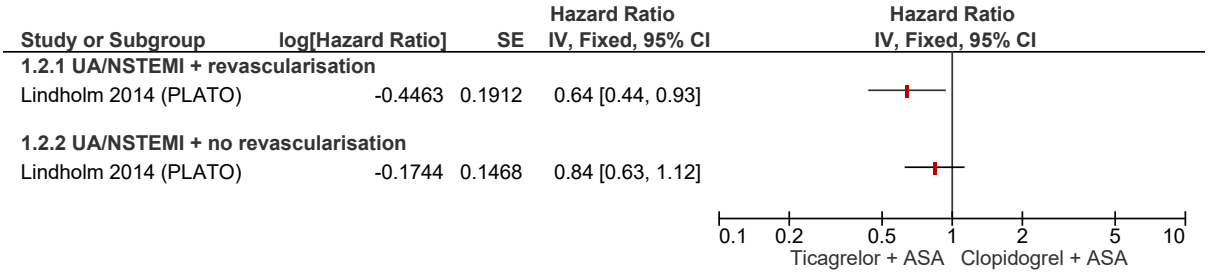


Figure 7: All-cause mortality at 30 days



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.64 (0.44, 0.92); UA/NSTEMI + no revascularisation – HR 0.84 (0.63, 1.11)

Figure 8: All-cause mortality at 1 year

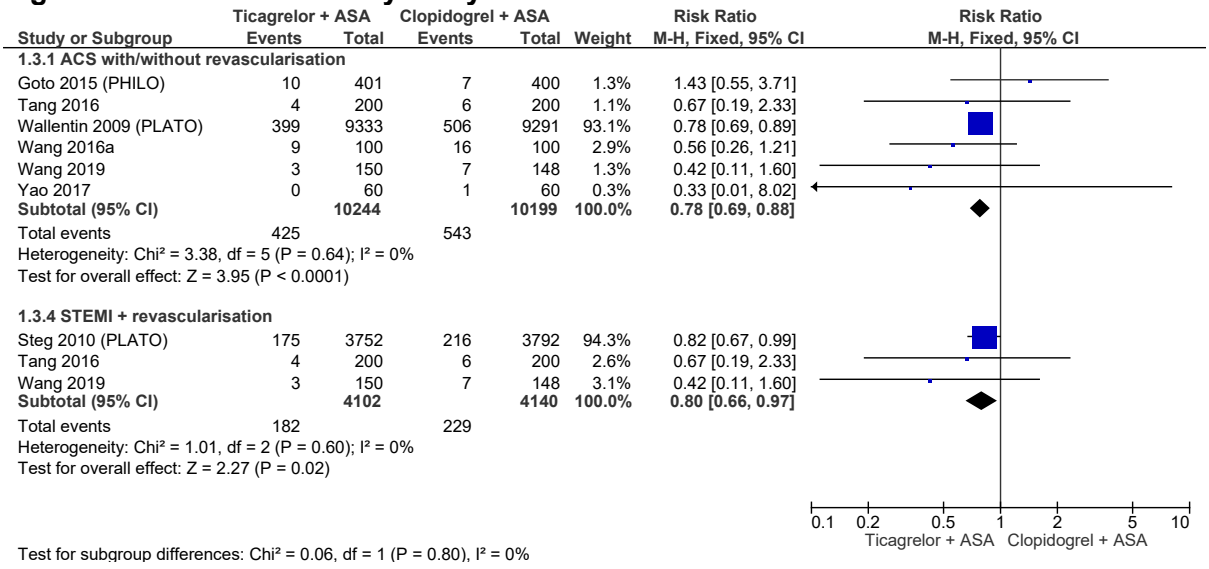
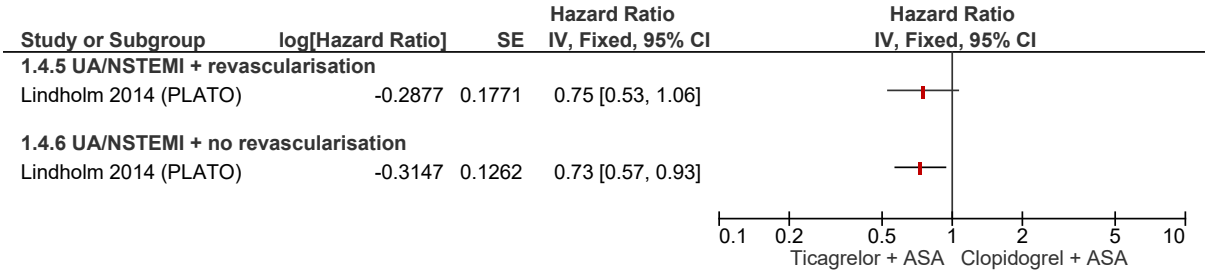


Figure 9: All-cause mortality at 1 year



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.75 (0.53, 1.06); UA/NSTEMI + no revascularisation – no difference

Figure 10: Cardiac mortality at 30 days

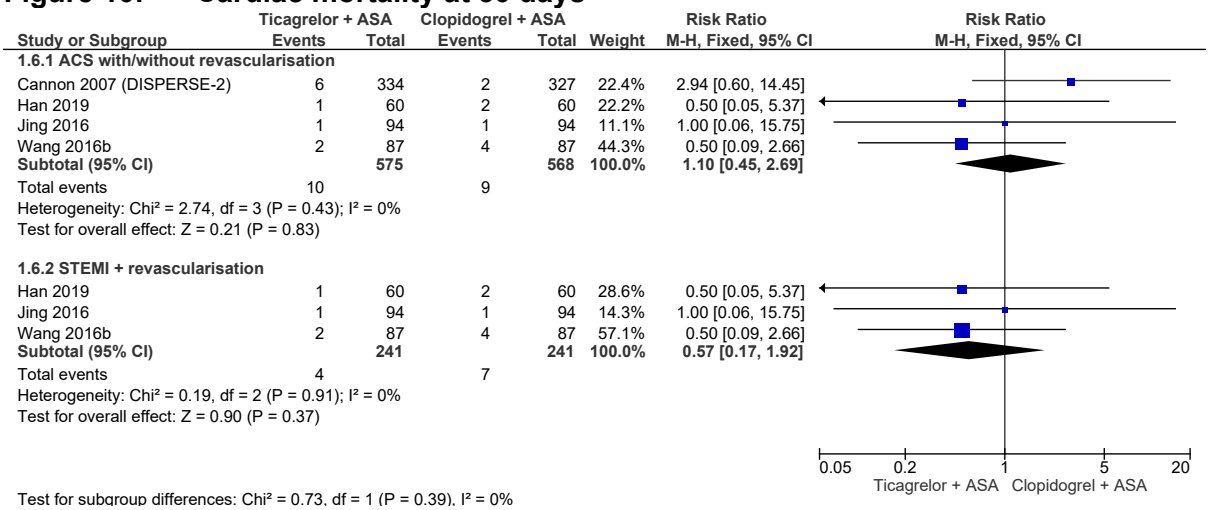
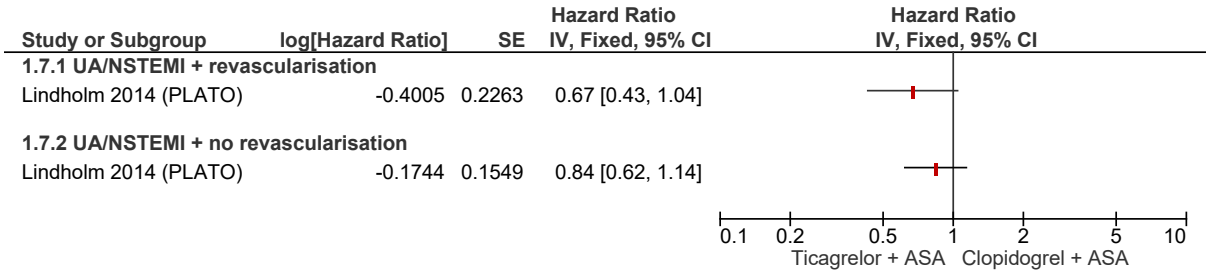
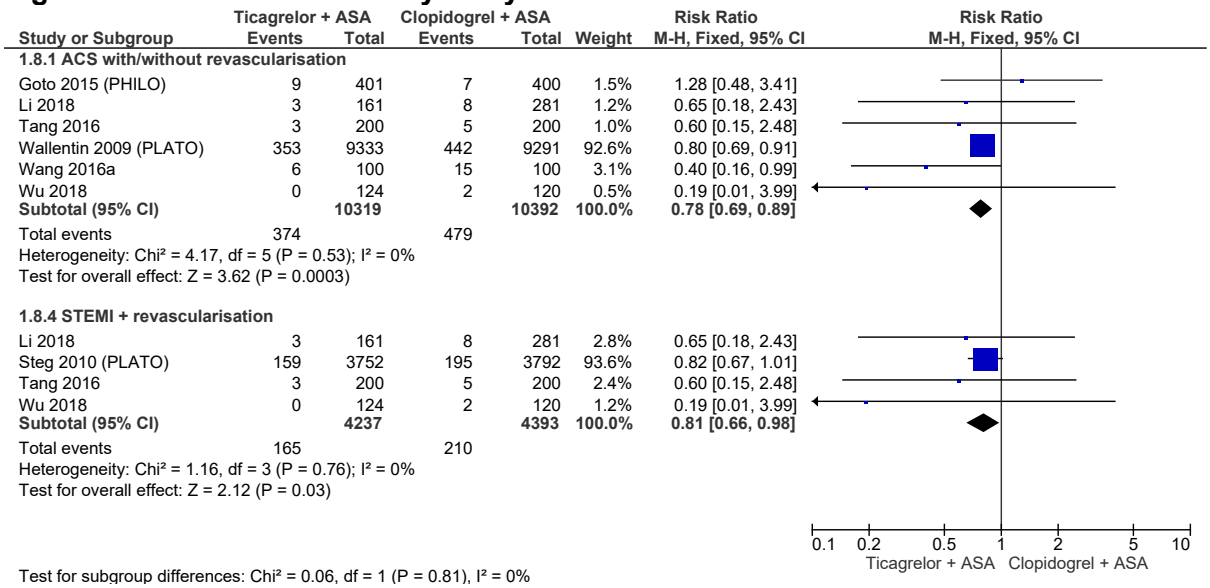


Figure 11: Cardiac mortality at 30 days



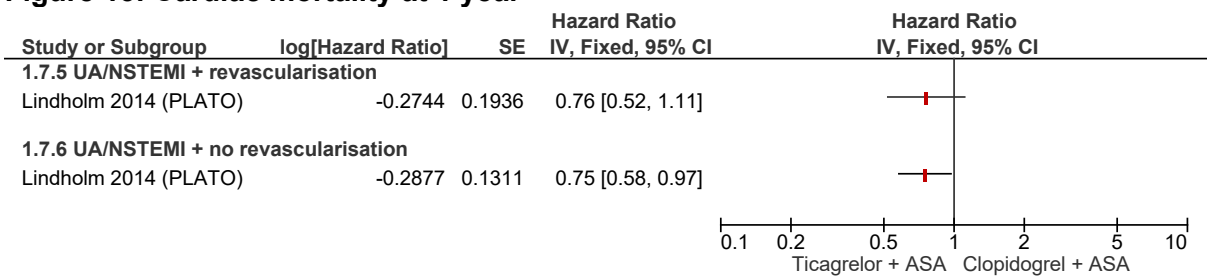
There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.67 (0.43, 1.02); UA/NSTEMI + no revascularisation – no difference

Figure 12: Cardiac mortality at 1 year



Goto 1 year; Tang 6 mos; Wallentin 1 year; Wang 1 year; Zhang 6 mos; Steg 1 year

Figure 13: Cardiac mortality at 1 year



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.76 (0.52, 1.13); UA/NSTEMI + no revascularisation – HR 0.75 (0.58, 0.98)

Figure 14: Re-infarction at 30 days

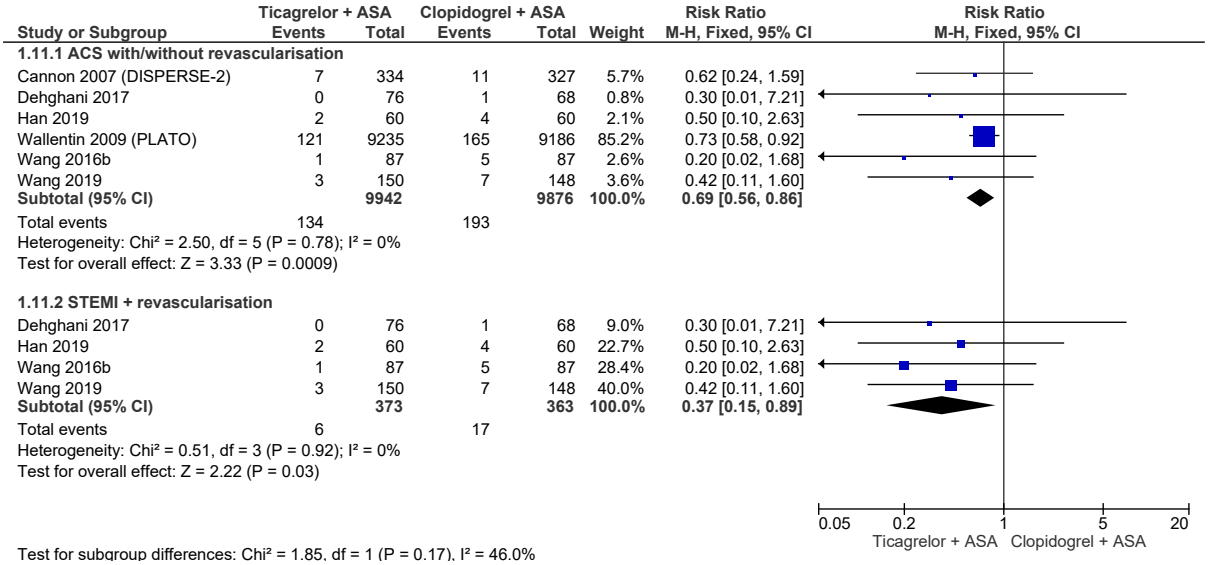
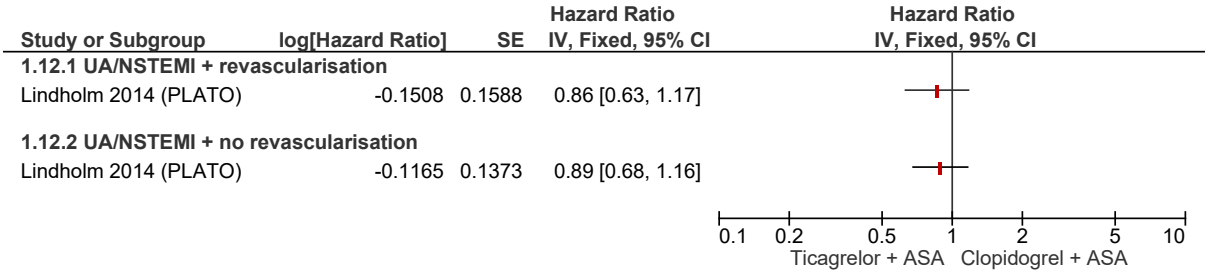


Figure 15: Re-infarction at 30 days



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.86 (0.63, 1.16); UA/NSTEMI + no revascularisation – HR 0.89 (0.68, 1.17)

Figure 16: Re-infarction at 1 year

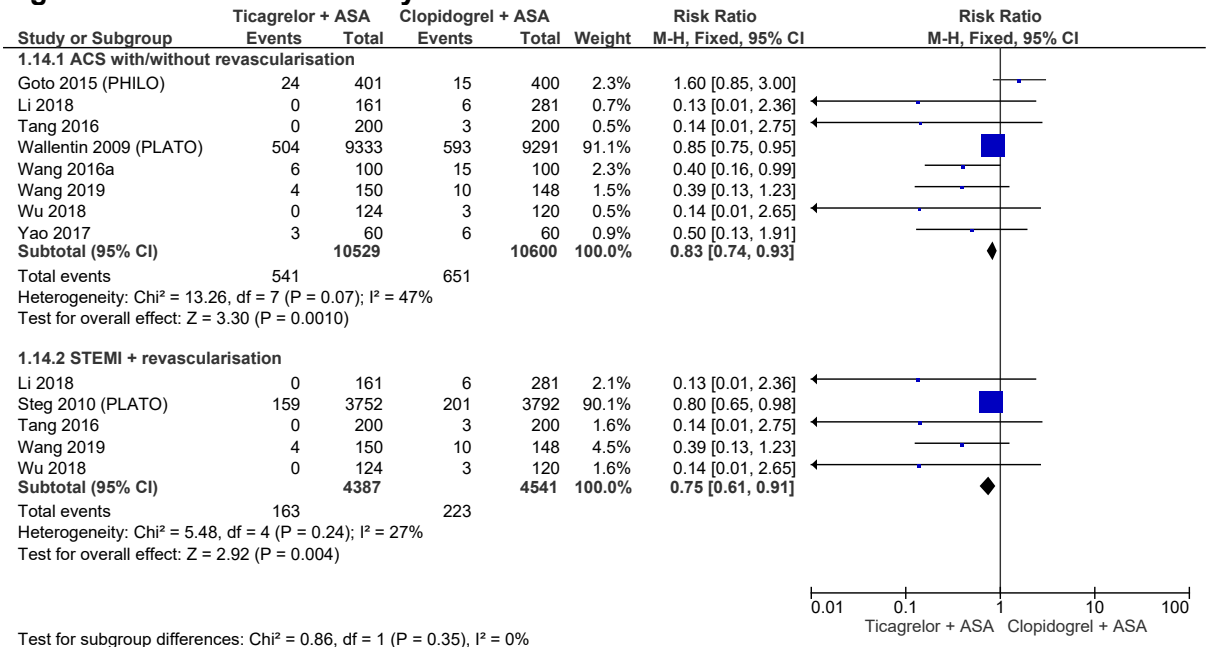
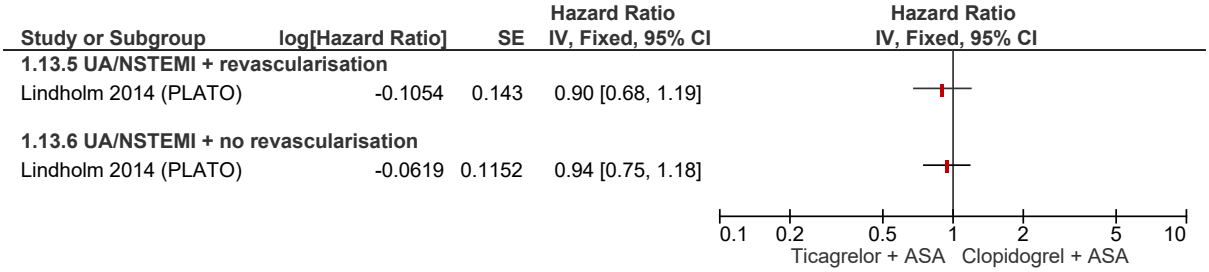
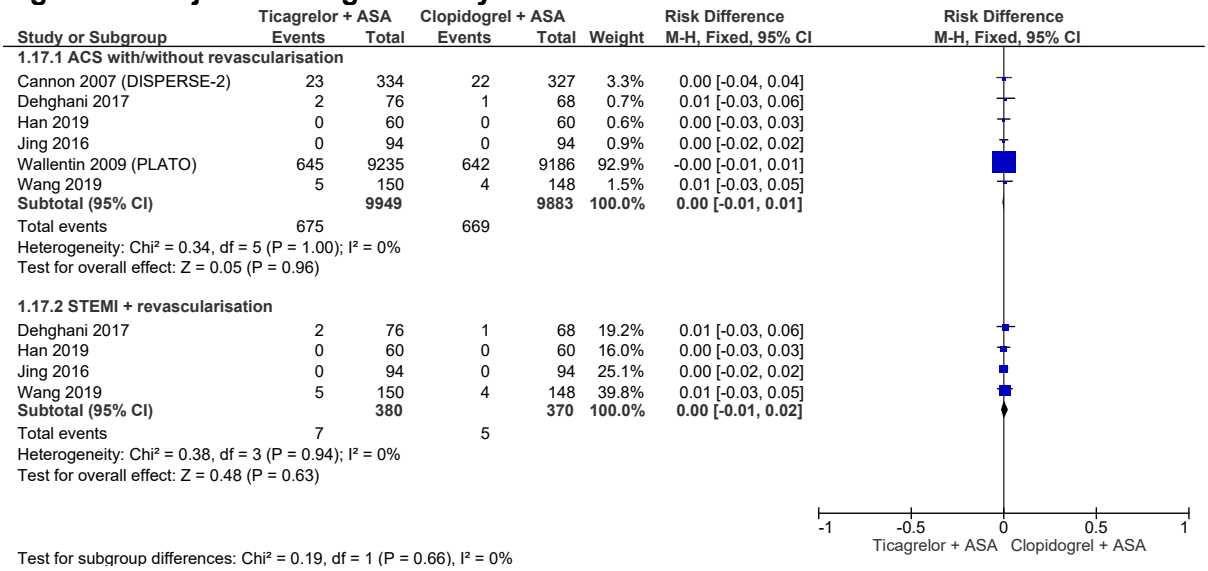


Figure 17: Re-infarction at 1 year



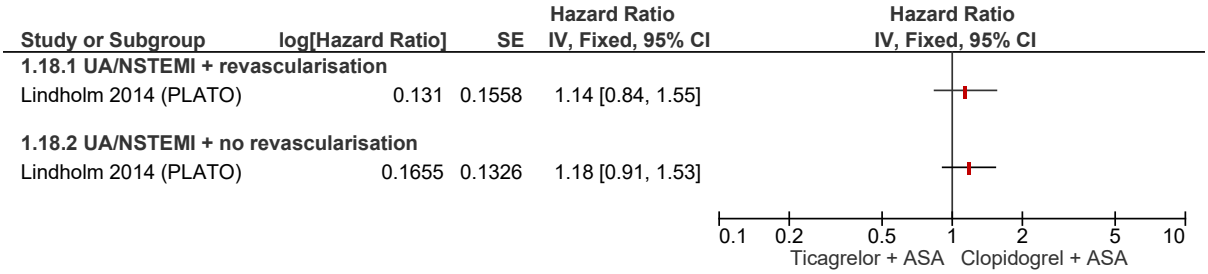
There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 0.90 (0.68, 1.21); UA/NSTEMI + no revascularisation – HR 0.94 (0.75, 1.17)

Figure 18: Major bleeding at 30 days



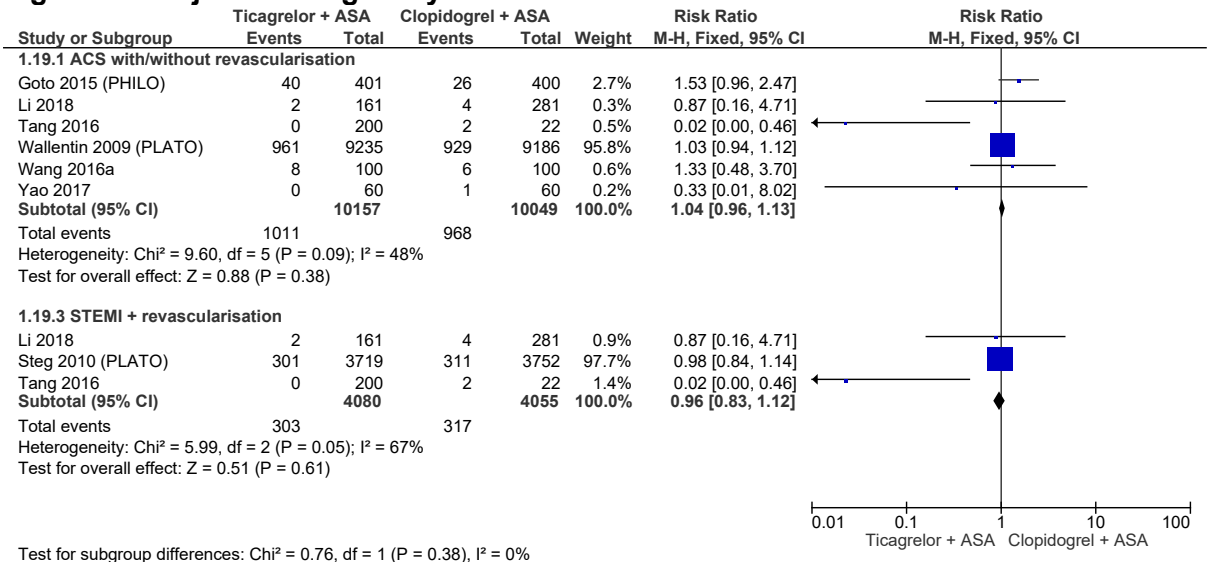
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%

Figure 19: Major bleeding at 30 days



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 1.14 (0.84, 1.56); UA/NSTEMI + no revascularisation – HR 1.18 (0.91, 1.54)

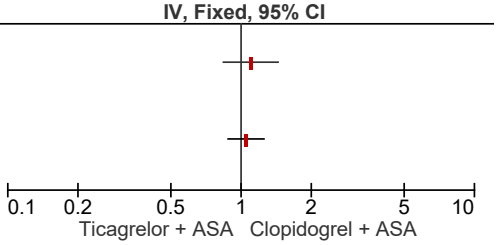
Figure 20: Major bleeding at 1 year



Test for subgroup differences: Chi² = 0.76, df = 1 (P = 0.38), I² = 0%

Figure 21: Major bleeding at 1 year

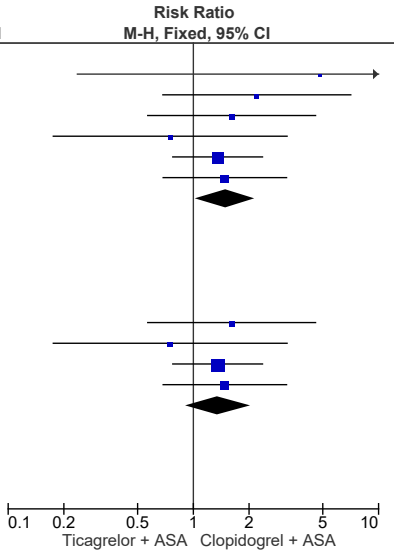
Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
1.17.5 UA/NSTEMI + revascularisation			
Lindholm 2014 (PLATO)	0.0953	0.1376	1.10 [0.84, 1.44]
1.17.6 UA/NSTEMI + no revascularisation			
Lindholm 2014 (PLATO)	0.0488	0.0901	1.05 [0.88, 1.25]



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – no difference – HR 1.05 (0.88, 1.26)

Figure 22: Minor bleeding at 30 days

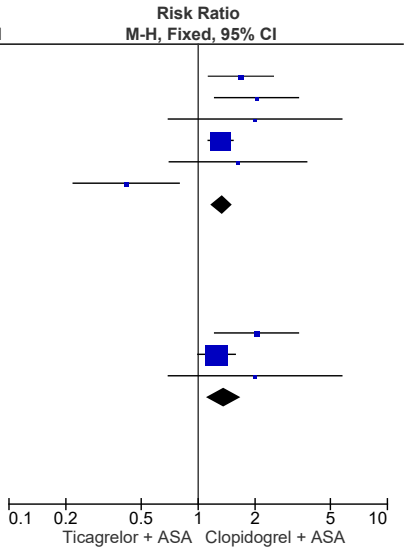
Study or Subgroup	Ticagrelor + ASA Events	Total	Clopidogrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.21.1 ACS with/without revascularisation						
Angiolillo 2016	2	51	0	49	1.2%	4.81 [0.24, 97.68]
Cannon 2007 (DISPERSE-2)	9	334	4	327	9.9%	2.20 [0.69, 7.08]
Dehghani 2017	9	76	5	68	12.9%	1.61 [0.57, 4.57]
Han 2019	3	60	4	60	9.8%	0.75 [0.18, 3.21]
Jing 2016	23	94	17	94	41.6%	1.35 [0.77, 2.36]
Wang 2019	15	150	10	148	24.6%	1.48 [0.69, 3.19]
Subtotal (95% CI)		**765**		**746**	**100.0%**	**1.49 [1.02, 2.16]**
Total events	61		40			
Heterogeneity: Chi² = 2.00, df = 5 (P = 0.85); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
1.21.2 STEMI + revascularisation						
Dehghani 2017	9	76	5	68	14.5%	1.61 [0.57, 4.57]
Han 2019	3	60	4	60	11.0%	0.75 [0.18, 3.21]
Jing 2016	23	94	17	94	46.8%	1.35 [0.77, 2.36]
Wang 2019	15	150	10	148	27.7%	1.48 [0.69, 3.19]
Subtotal (95% CI)		**380**		**370**	**100.0%**	**1.36 [0.91, 2.02]**
Total events	50		36			
Heterogeneity: Chi² = 0.79, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 1.51 (P = 0.13)						



Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%

Figure 23: Minor bleeding at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Clopidogrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.22.1 ACS with/without revascularisation						
Goto 2015 (PHILO)	59	401	35	400	9.3%	1.68 [1.13, 2.49]
Li 2018	28	161	24	281	4.6%	2.04 [1.22, 3.39]
Tang 2016	10	200	5	200	1.3%	2.00 [0.70, 5.75]
Wallentin 2009 (PLATO)	378	9235	286	9186	76.2%	1.31 [1.13, 1.53]
Wang 2016a	13	100	8	100	2.1%	1.63 [0.70, 3.75]
Yao 2017	10	60	24	60	6.4%	0.42 [0.22, 0.79]
Subtotal (95% CI)		**10157**		**10227**	**100.0%**	**1.34 [1.18, 1.53]**
Total events	498		382			
Heterogeneity: Chi² = 17.28, df = 5 (P = 0.004); I² = 71%						
Test for overall effect: Z = 4.45 (P < 0.00001)						
1.22.3 STEMI + revascularisation						
Li 2018	28	161	24	281	11.6%	2.04 [1.22, 3.39]
Steg 2010 (PLATO)	160	3719	129	3752	85.1%	1.25 [1.00, 1.57]
Tang 2016	10	200	5	200	3.3%	2.00 [0.70, 5.75]
Subtotal (95% CI)		**4080**		**4233**	**100.0%**	**1.37 [1.12, 1.68]**
Total events	198		158			
Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 3.02 (P = 0.003)						



Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.87), I² = 0%

Figure 24: Bleeding (type not specified) at 1 year

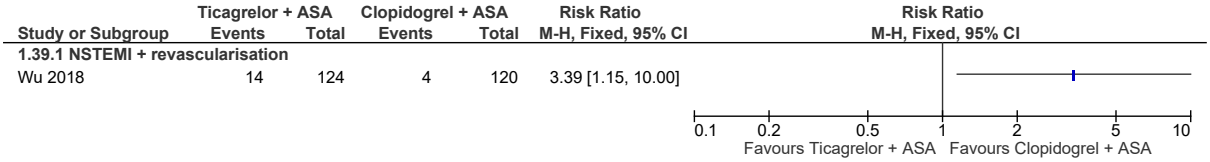


Figure 25: Stroke (type not specified) at 30 days

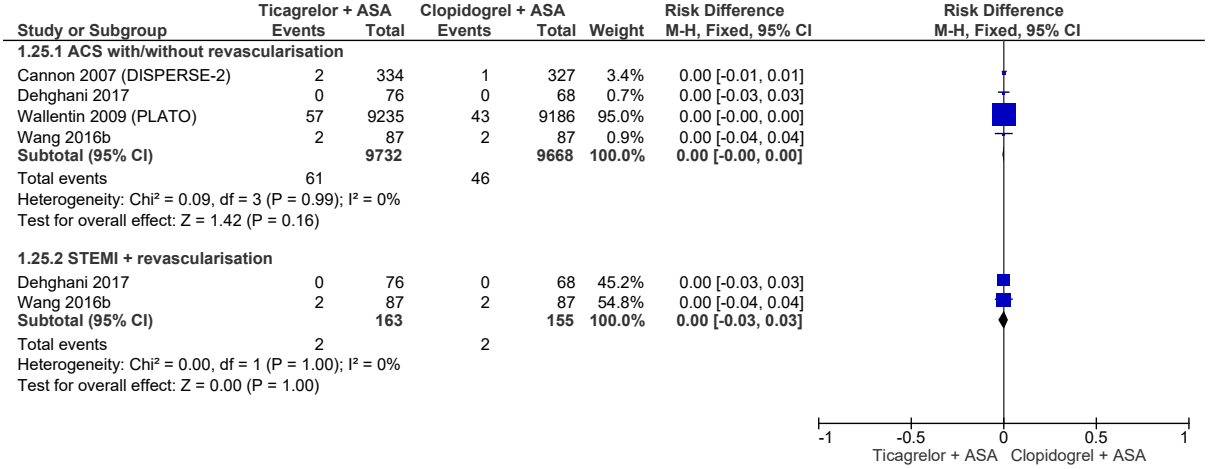
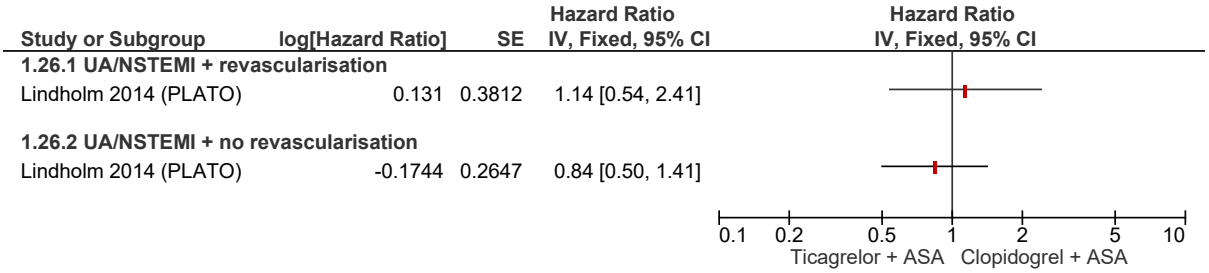


Figure 26: Stroke (type not specified) at 30 days



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 1.14 (0.54, 2.40); UA/NSTEMI + no revascularisation – HR 0.84 (0.50, 1.41)

Figure 27: Stroke (type not specified) at 1 year

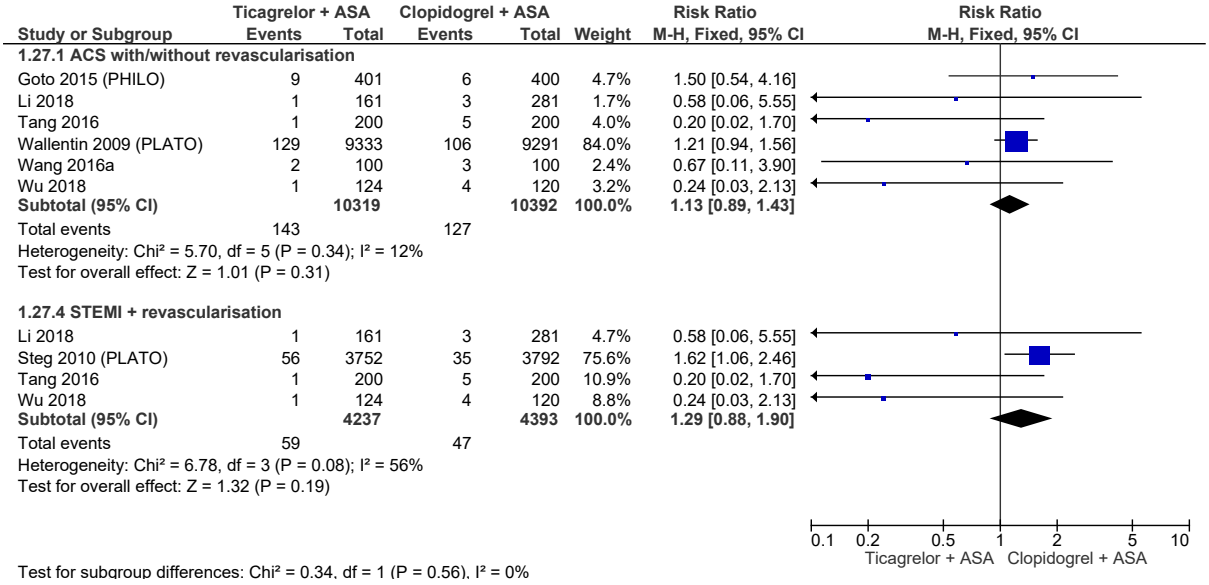
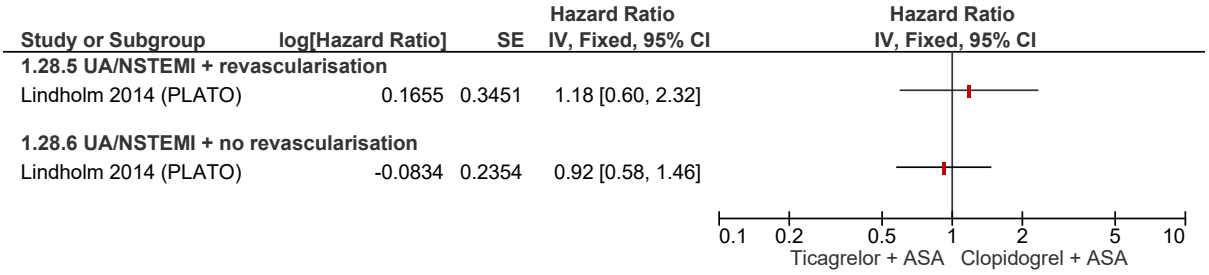


Figure 28: Stroke (type not specified) at 1 year



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager. UA/NSTEMI + revascularisation – HR 1.18 (0.60, 2.34); UA/NSTEMI + no revascularisation – no difference

Figure 29: Need for revascularisation at 30 days

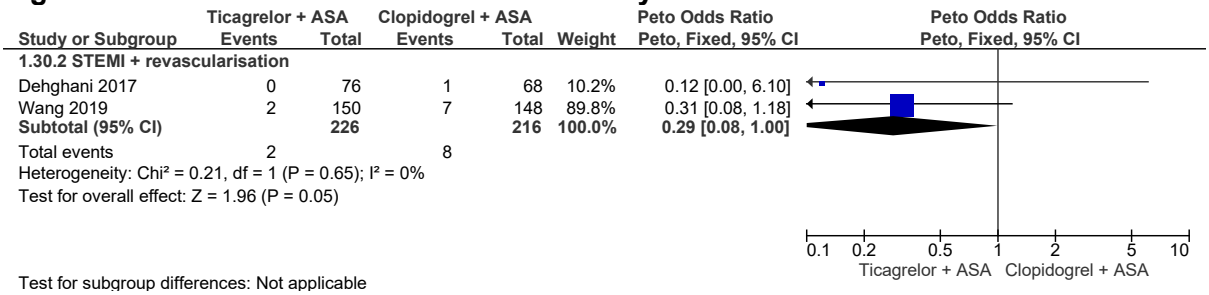


Figure 30: Need for revascularisation at 1 year

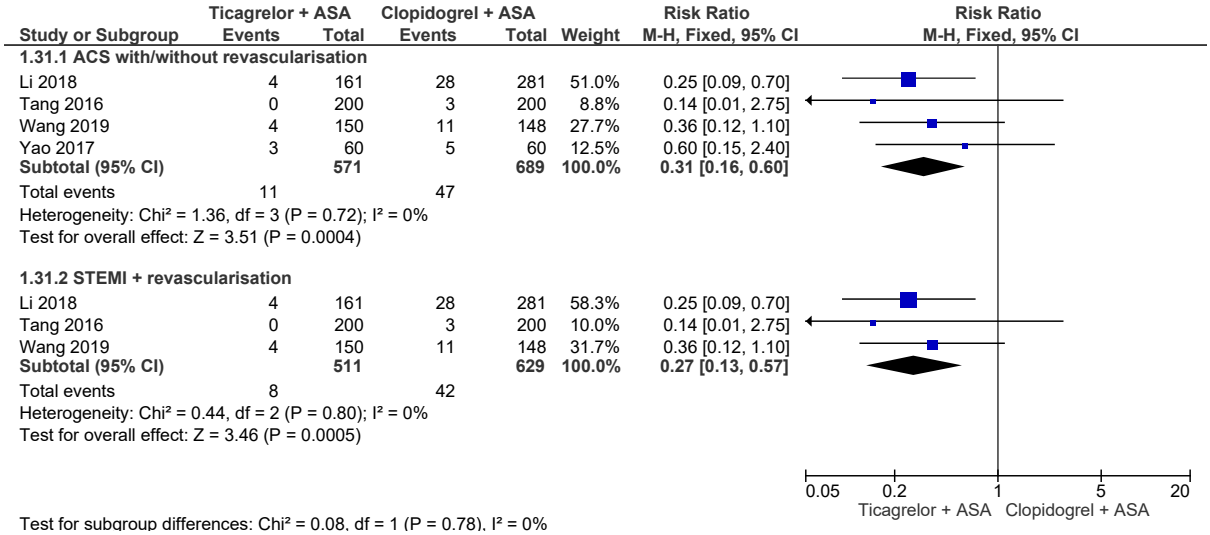


Figure 31: Stent thrombosis (type not specified) at 30 days

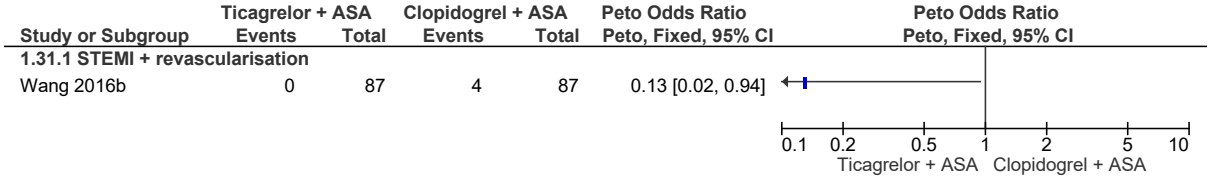


Figure 32: Stent thrombosis (probable or definite) at 1 year

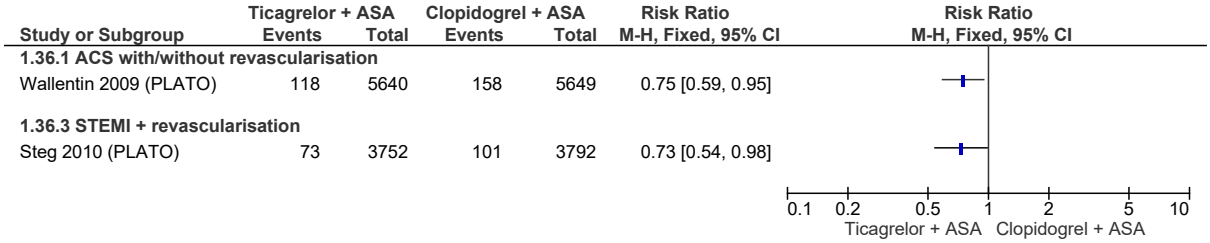


Figure 33: Stent thrombosis (type not specified) (ACS with/without revascularisation at 1 year

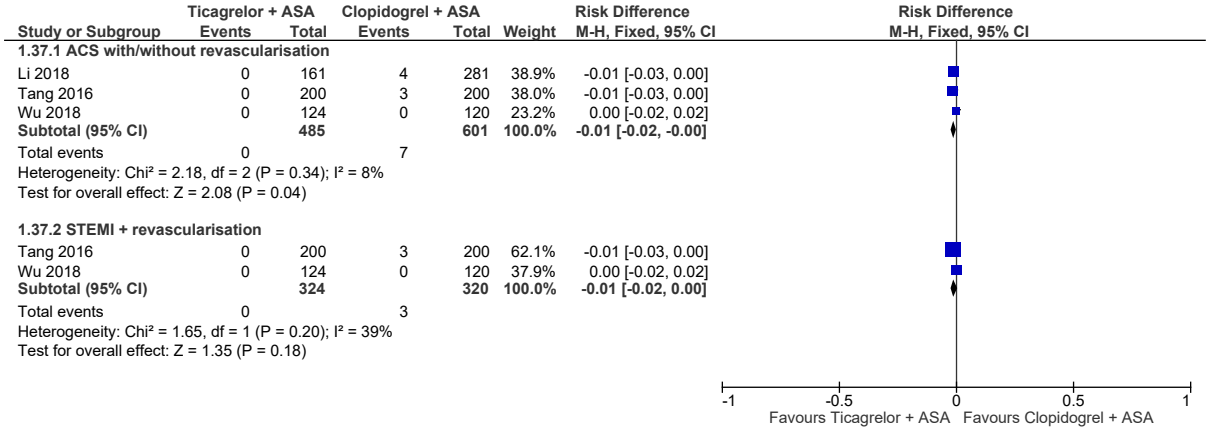


Figure 34: Stent thrombosis (type not specified) (NSTEMI + revascularisation) at 1 year

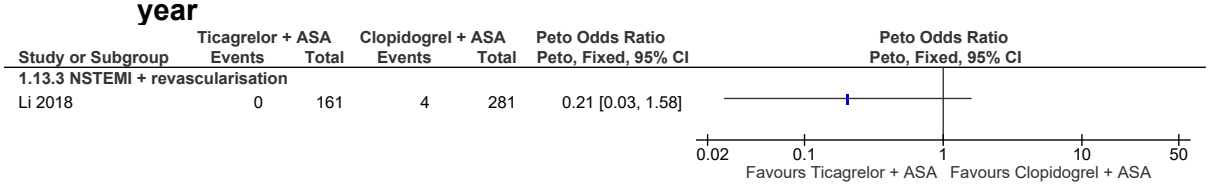


Figure 35: Breathing adverse effects at 30 days

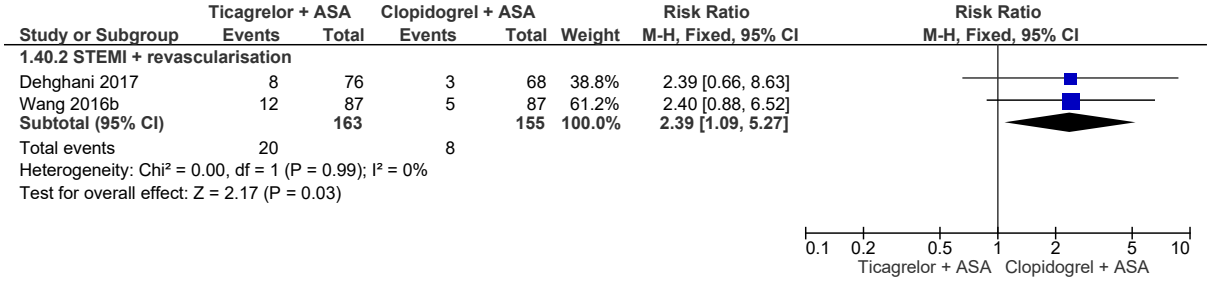


Figure 36: Breathing adverse effects at 1 year

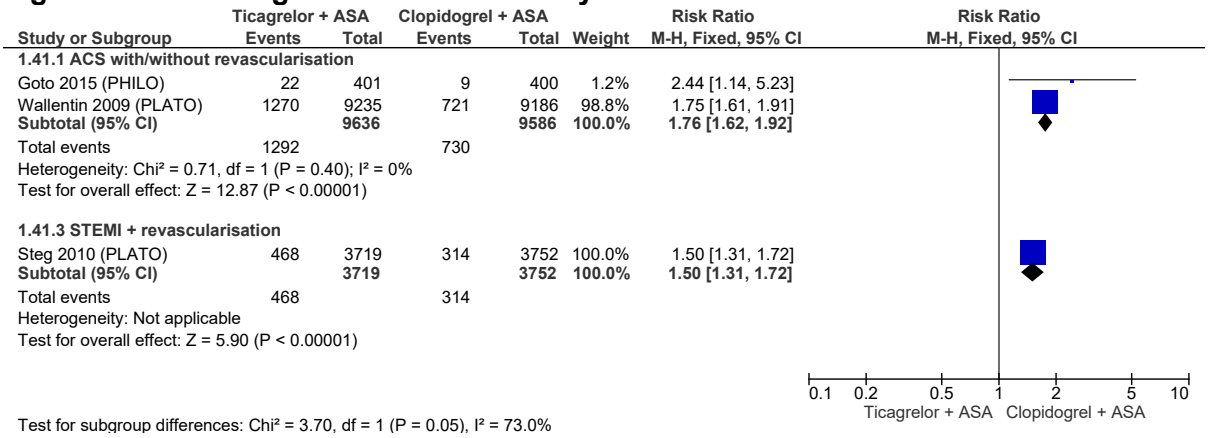


Figure 37: Bradycardic adverse effects at 30 days

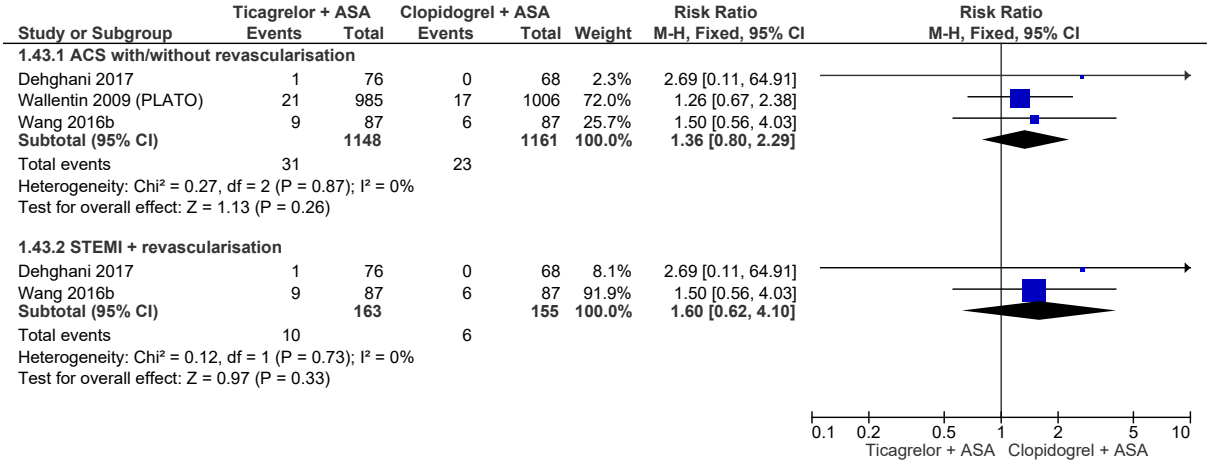


Figure 38: Bradycardic adverse effects at 1 year

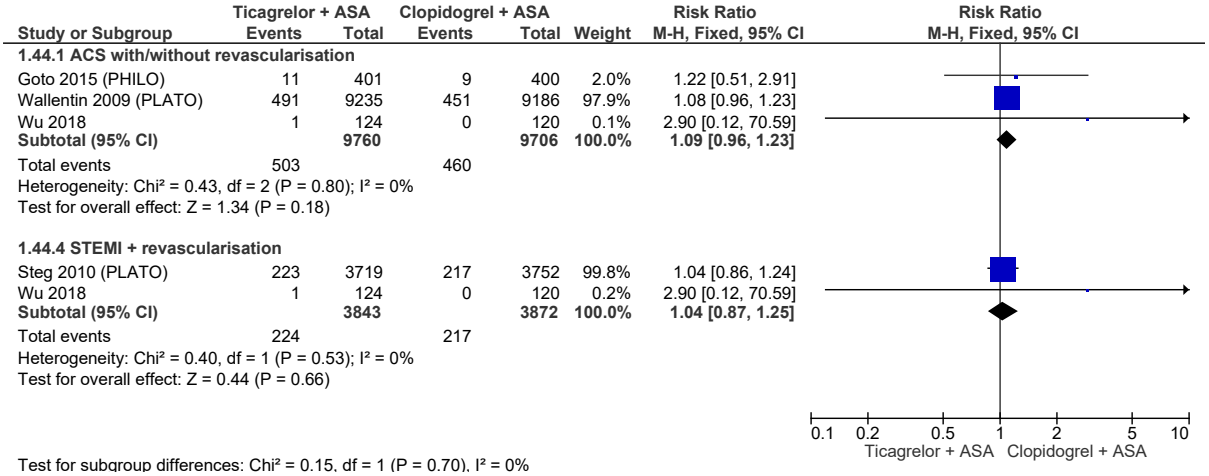


Figure 39: Other adverse effects at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Clopidogrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.45.1 ACS with/without revascularisation						
Angiolillo 2016	15	51	9	49	26.3%	1.60 [0.77, 3.31]
Dehghani 2017	13	76	12	68	36.3%	0.97 [0.48, 1.98]
Wang 2016b	17	87	13	87	37.3%	1.31 [0.68, 2.53]
Subtotal (95% CI)		**214**		**204**	**100.0%**	**1.26 [0.85, 1.88]**
Total events	45		34			
Heterogeneity: Chi² = 0.95, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.26)						
1.45.2 STEMI + revascularisation						
Dehghani 2017	13	76	12	68	49.4%	0.97 [0.48, 1.98]
Wang 2016b	17	87	13	87	50.6%	1.31 [0.68, 2.53]
Subtotal (95% CI)		**163**		**155**	**100.0%**	**1.14 [0.70, 1.85]**
Total events	30		25			
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						

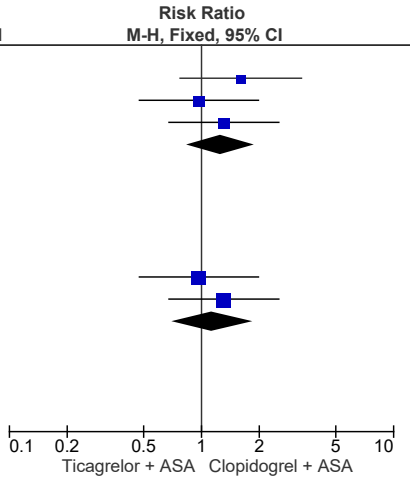


Figure 40: Other adverse effects at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Clopidogrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.60.1 ACS with/without revascularisation						
Goto 2015 (PHILO)	327	401	337	400	69.2%	0.97 [0.91, 1.03]
Wallentin 2009 (PLATO)	167	9235	142	9186	29.2%	1.17 [0.94, 1.46]
Yao 2017	5	60	8	60	1.6%	0.63 [0.22, 1.80]
Subtotal (95% CI)		**9696**		**9646**	**100.0%**	**1.02 [0.94, 1.11]**
Total events	499		487			
Heterogeneity: Chi² = 5.05, df = 2 (P = 0.08); I² = 60%						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.60.2 STEMI + revascularisation						
Steg 2010 (PLATO)	77	3719	62	3752	100.0%	1.25 [0.90, 1.75]
Subtotal (95% CI)		**3719**		**3752**	**100.0%**	**1.25 [0.90, 1.75]**
Total events	77		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.33 (P = 0.18)						

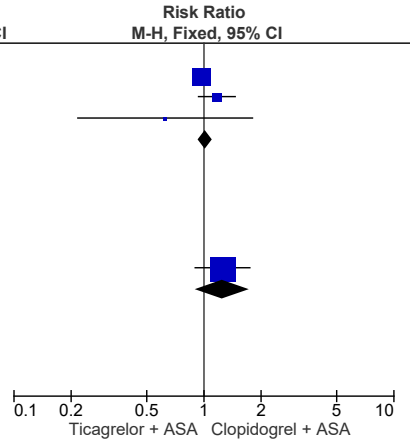
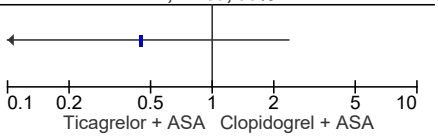


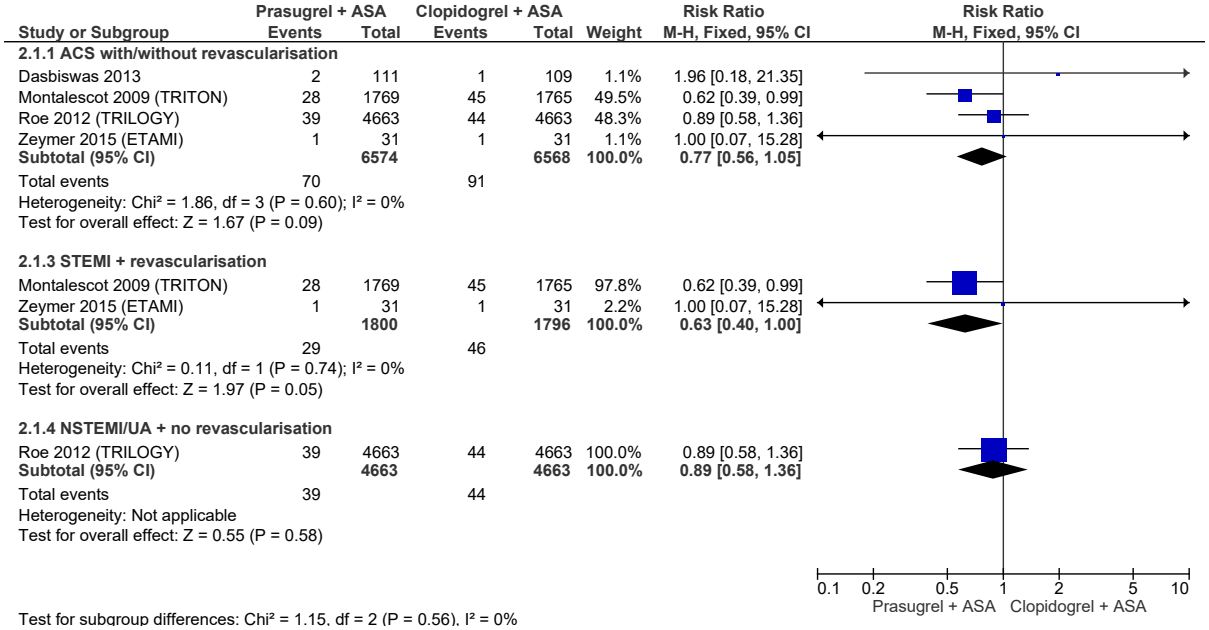
Figure 41: Unplanned urgent readmission at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Clopidogrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
1.77.1 STEMI + revascularisation					
Dehghani 2017	2	76	4	68	0.45 [0.08, 2.37]



E.2 Prasugrel + ASA versus clopidogrel + ASA

Figure 42: All-cause mortality at 30 days



Test for subgroup differences: Chi² = 1.15, df = 2 (P = 0.56), I² = 0%

Figure 43: All-cause mortality at 1 year

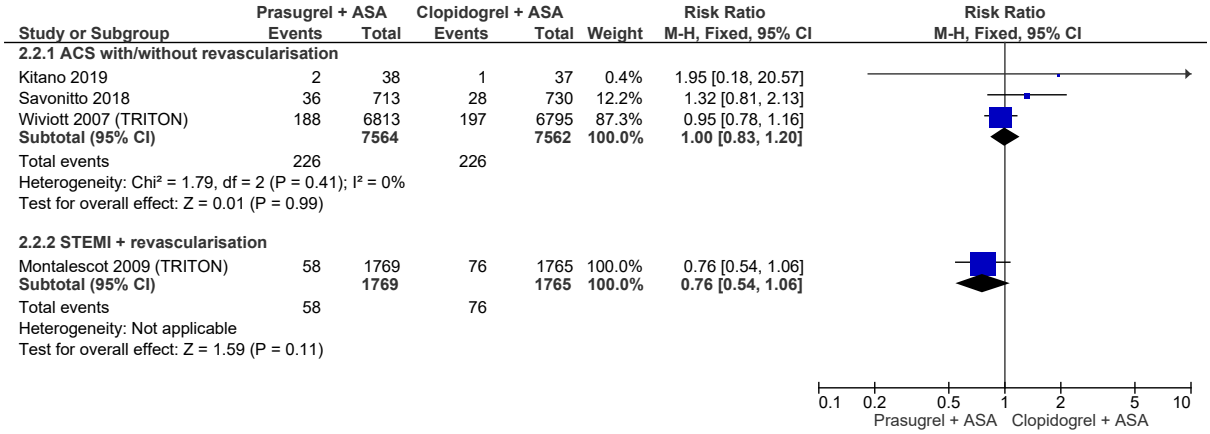


Figure 44: Cardiac mortality at 30 days

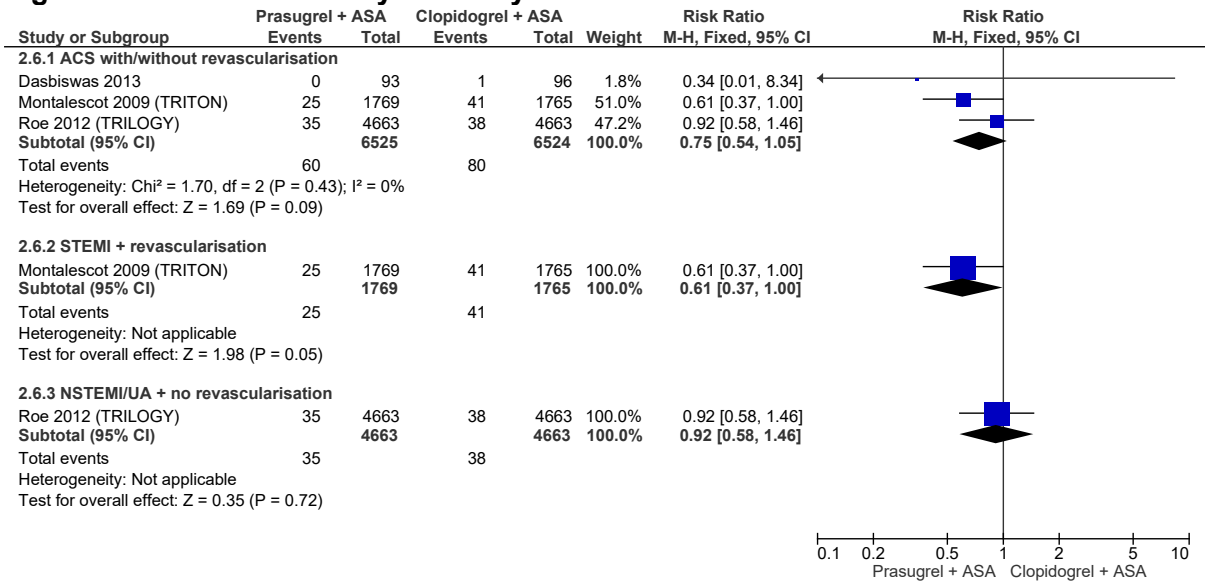


Figure 45: Cardiac mortality at 1 year

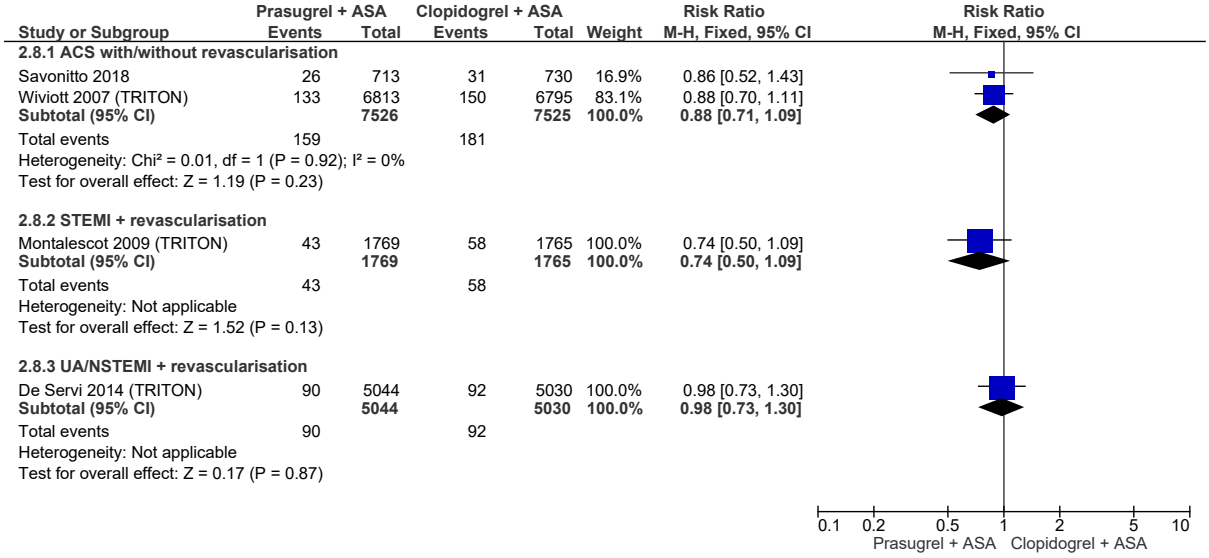


Figure 46: Cardiac mortality (people aged <75 years) at 1 year

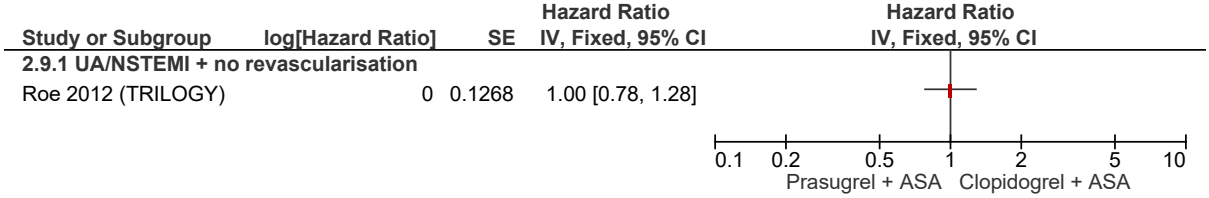


Figure 47: Re-infarction at 30 days (ACS with/without revascularisation and STEMI + revascularisation)

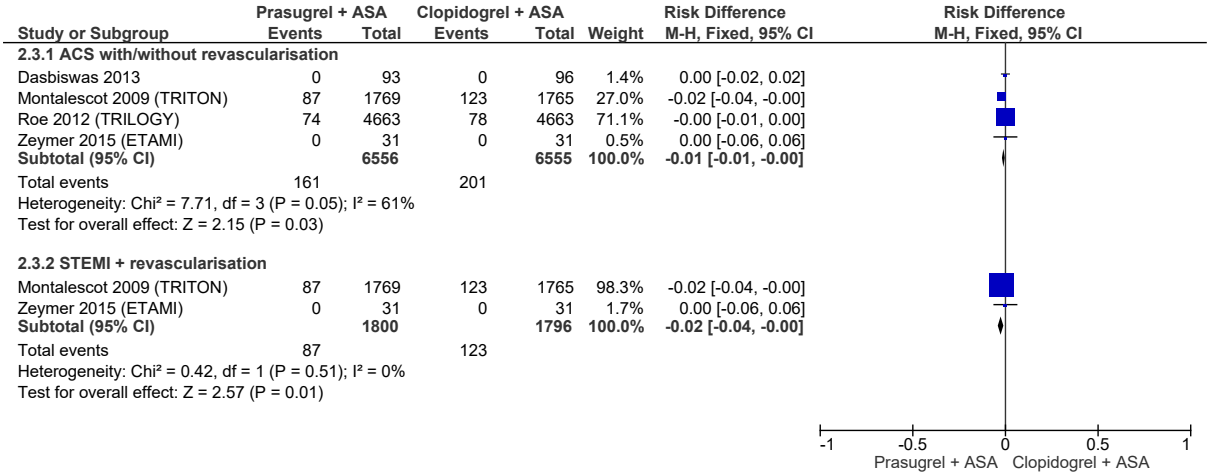


Figure 48: Re-infarction at 30 days (UA/NSTEMI + no revascularisation

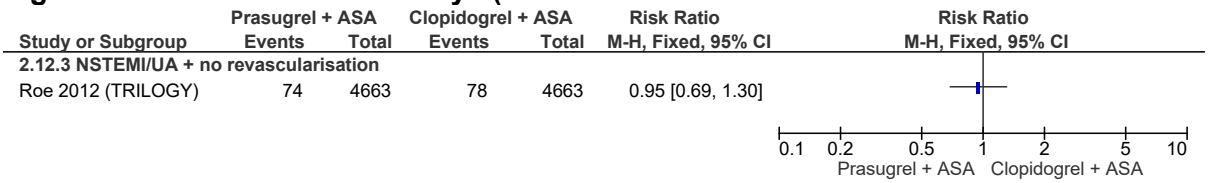


Figure 49: Re-infarction at 1 year

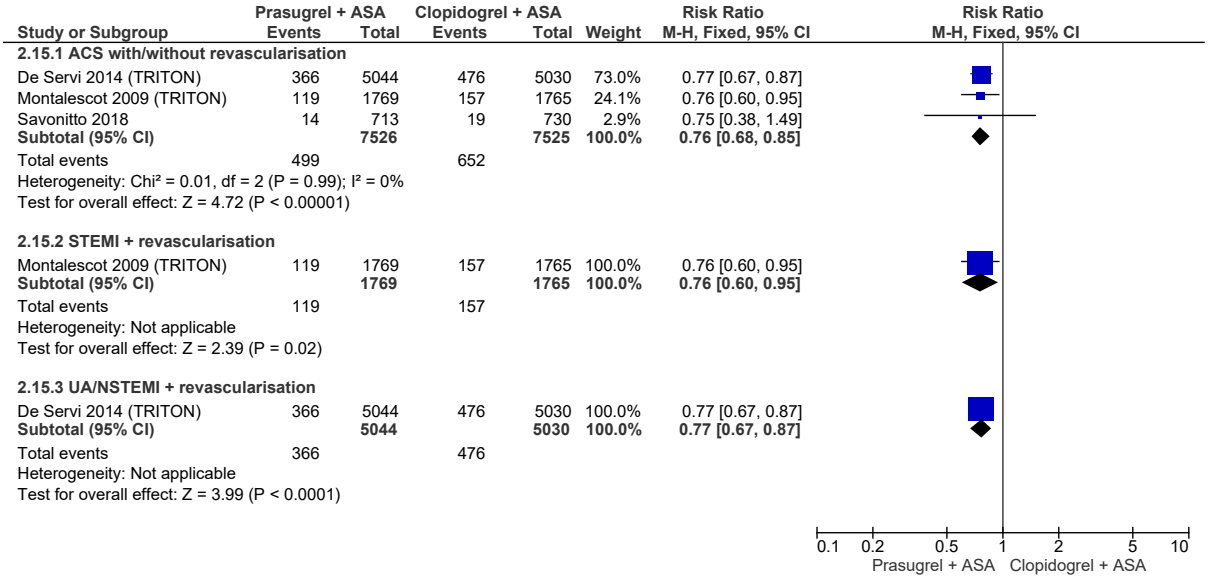
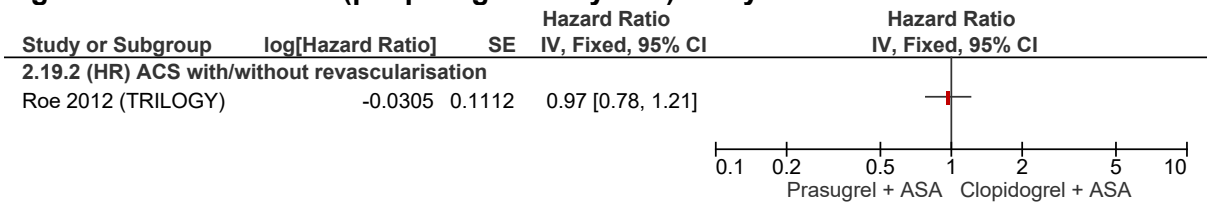


Figure 50: Re-infarction (people aged <75 years) at 1 year



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager - HR 0.97 (0.78, 1.19)

Figure 51: Major bleeding at 30 days (ACS with/without revascularisation)

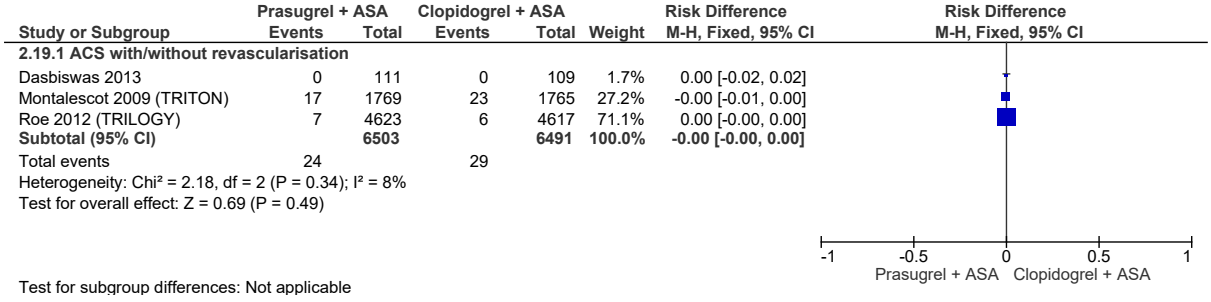


Figure 52: Major bleeding at 30 days (STEMI + revascularisation and UA/NSTEMI+ revascularisation

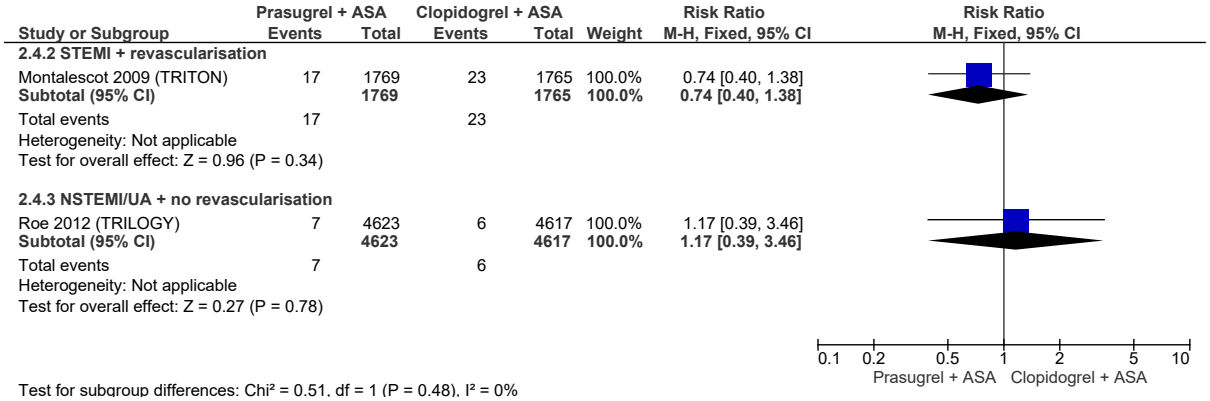


Figure 53: Bleeding (major and minor) at 30 days

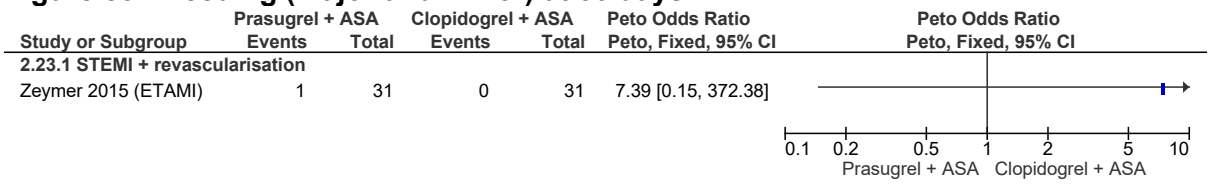


Figure 54: Major bleeding at 1 year

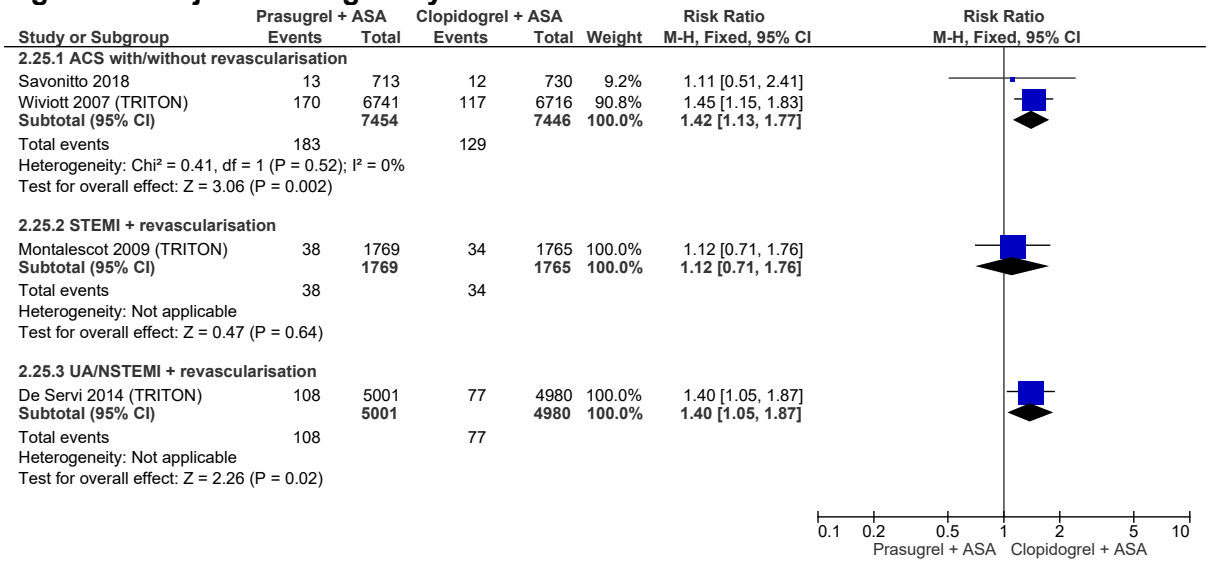


Figure 55: Minor bleeding at 30 days

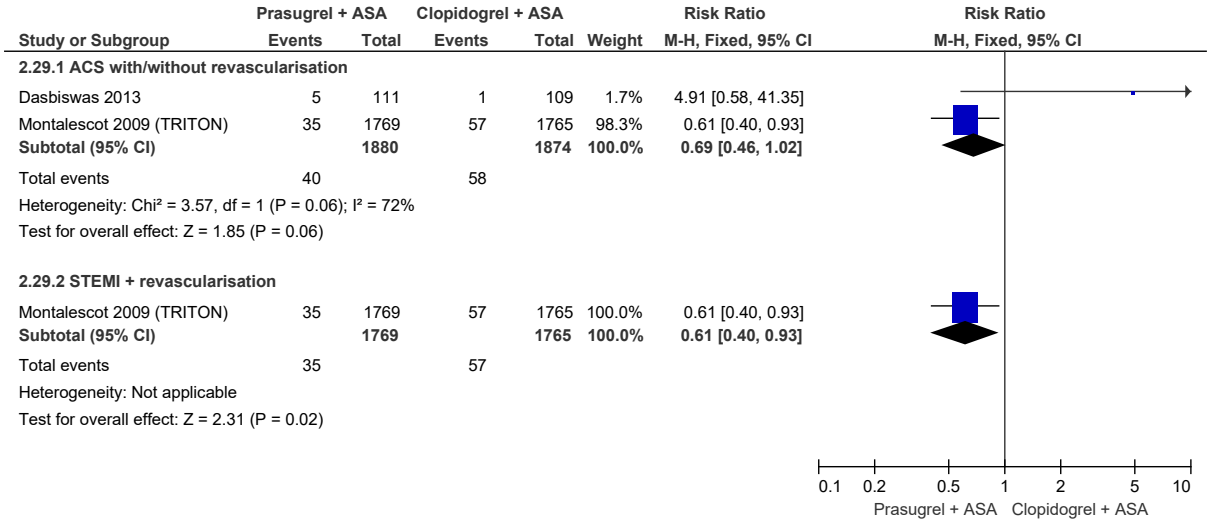


Figure 56: Minor bleeding at 1 year

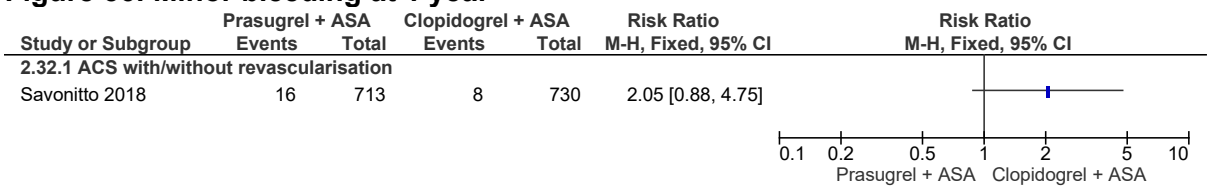
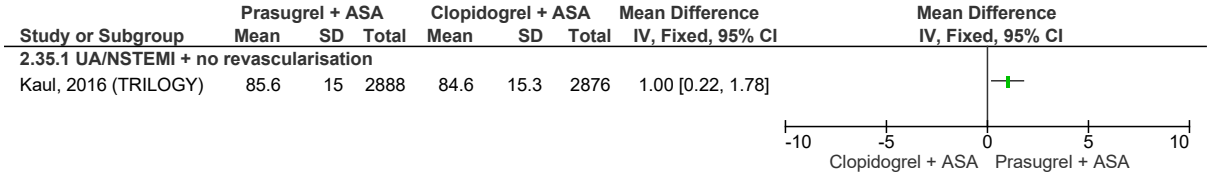
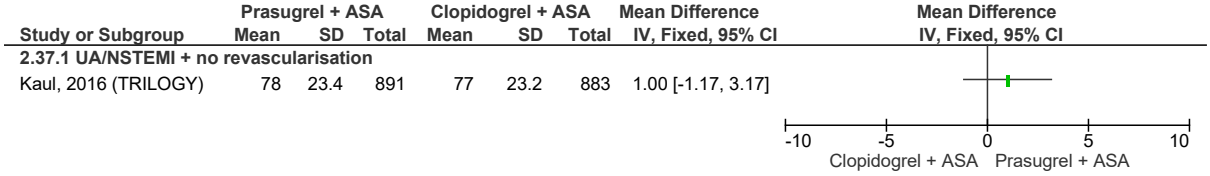


Figure 57: Health-related quality of life (EQ5D) (people aged <75 years) at 1 year, scale range: 0-100 (higher is better)



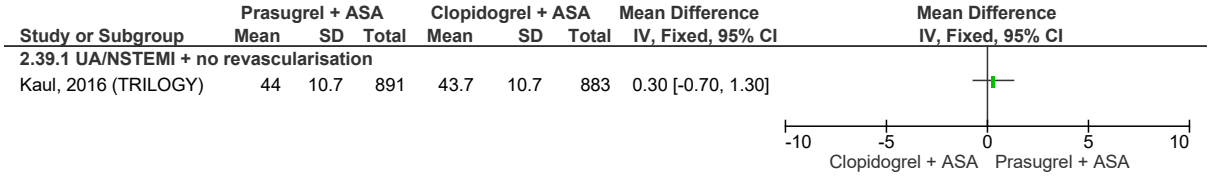
Note: final scores

Figure 58: Health-related quality of life (SAQ Physical) (people aged <75 years) at 1 year, scale range: 0-100 (higher is better)



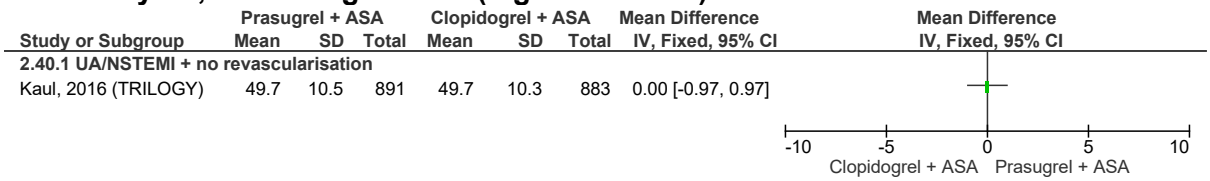
Note: final scores

Figure 59: Health-related quality of life (SF-12 Physical) (people aged <75 years) at 1 year, scale range: 0-100 (higher is better)



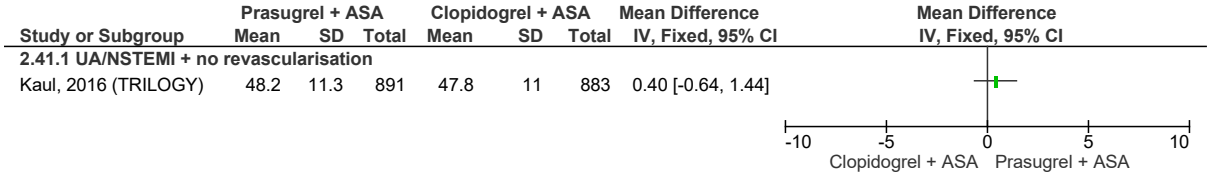
Note: final scores

Figure 60: Health-related quality of life (SF-12 Mental) (people aged <75 years) at 1 year, scale range: 0-100 (higher is better)



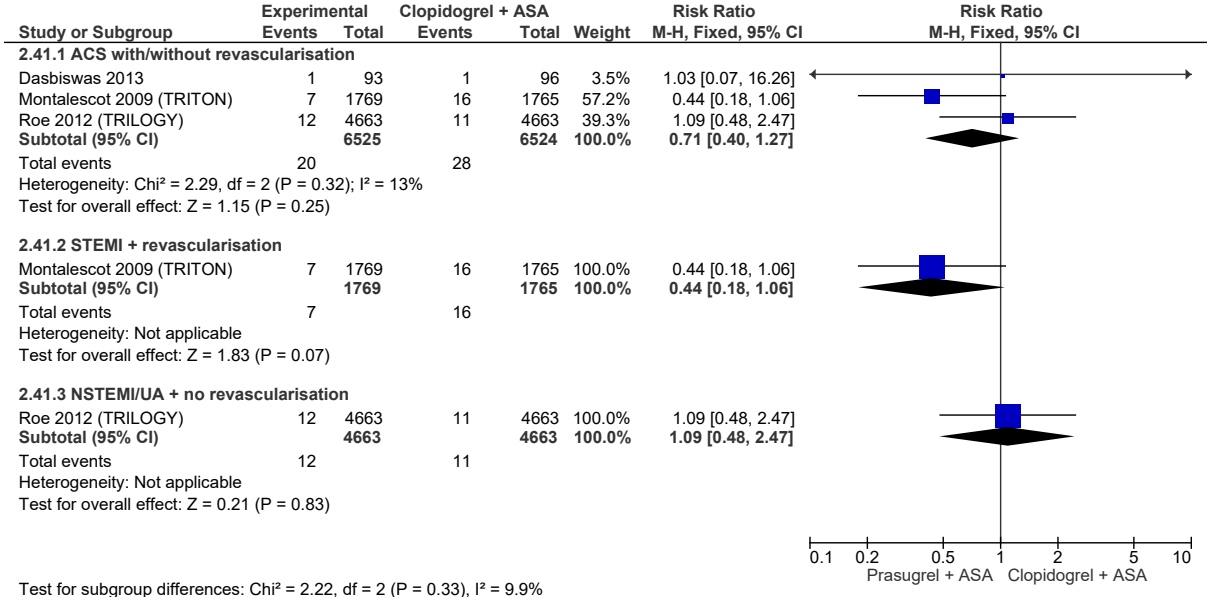
Note: final scores

Figure 61: Health-related quality of life (SF-36 Mental) (people aged <75 years) at 1 year, scale range: 0-100 (higher is better)



Note: final scores

Figure 62: Stroke (type not specified) at 30 days



Test for subgroup differences: Chi² = 2.22, df = 2 (P = 0.33), I² = 9.9%

Figure 63: Stroke (type not specified) at 1 year

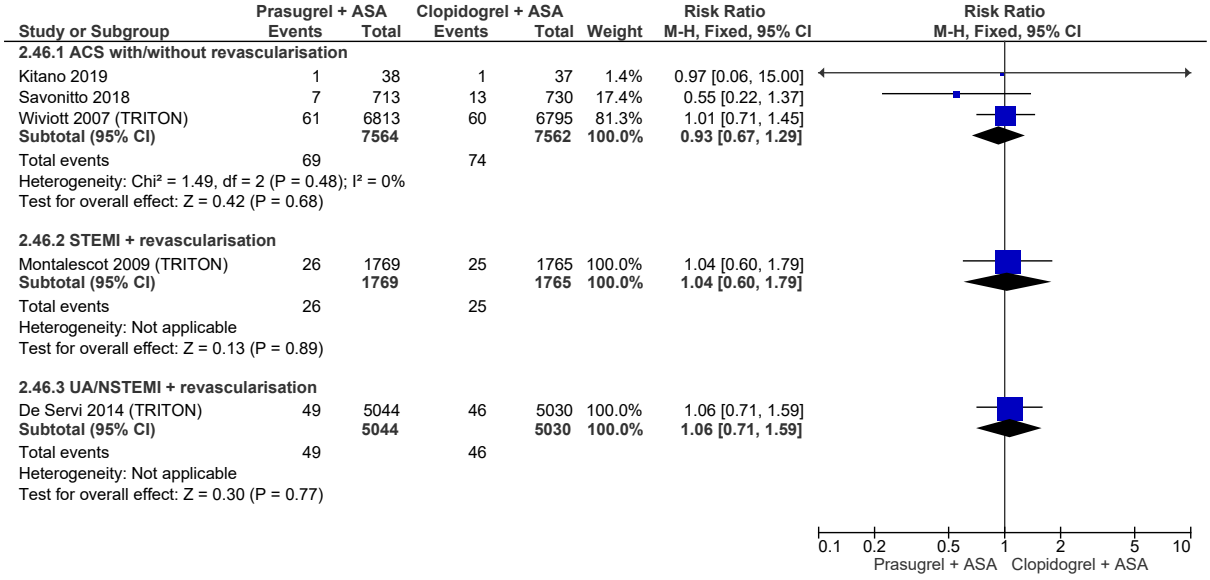
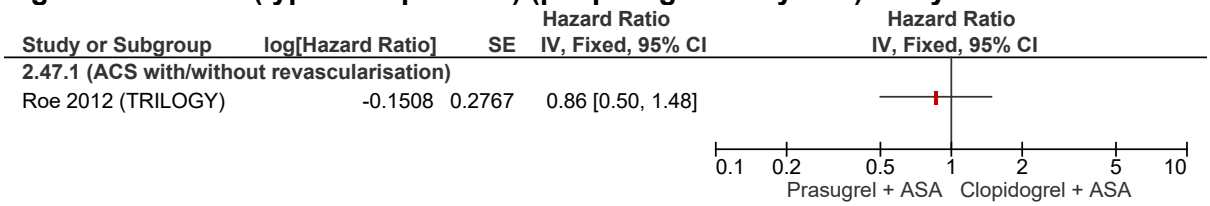


Figure 64: Stroke (type not specified) (people aged <75 years) at 1 year



There is a minor difference between the hazard ratio reported within the trial publication and hazard ratio reported in this review. Upper confidence interval could not be edited in Review Manager - HR 0.86 (0.50, 1.47)

Figure 65: Need for revascularisation at 30 days (ACS with/without revascularisation)

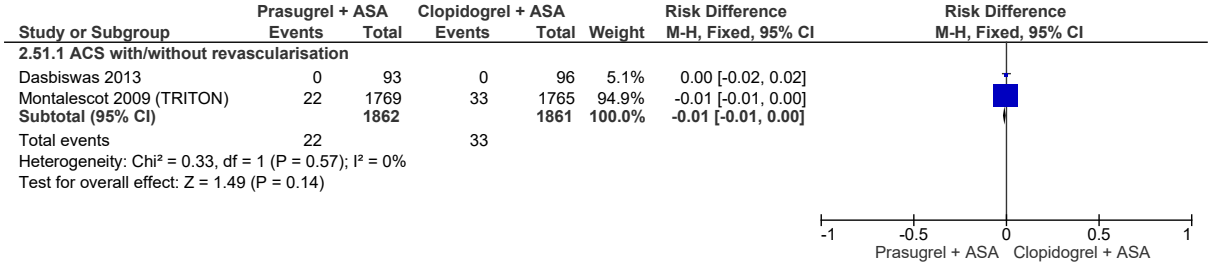


Figure 66: Need for revascularisation at 30 days (STEMI + revascularisation)

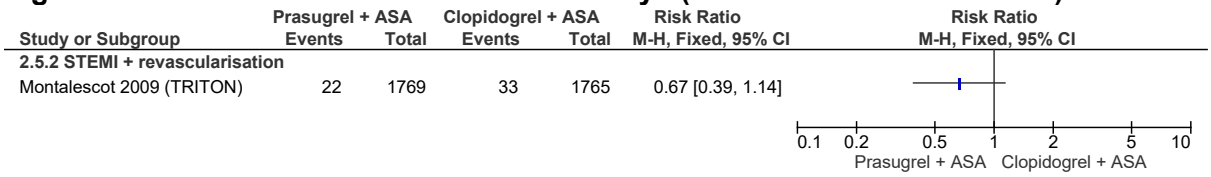


Figure 67: Need for revascularisation at 1 year

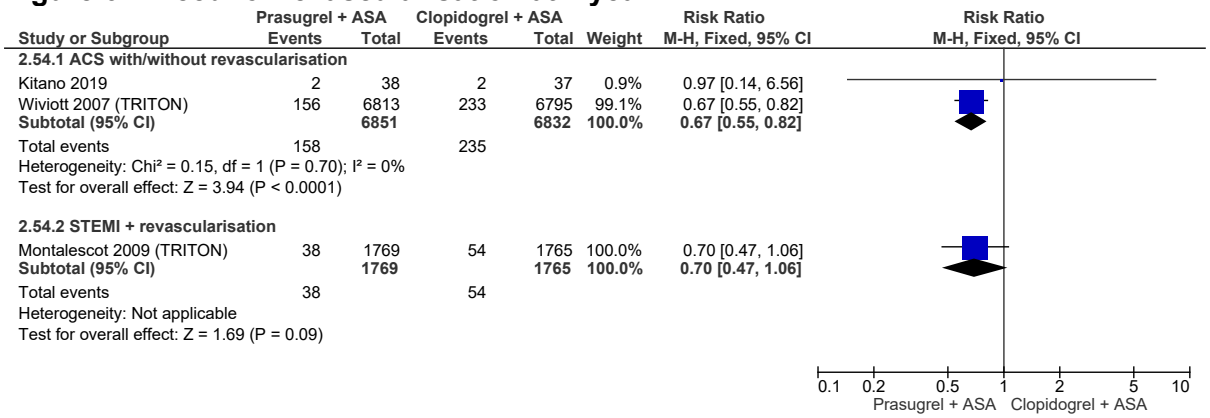


Figure 68: Stent thrombosis (definite or probable) at 30 days

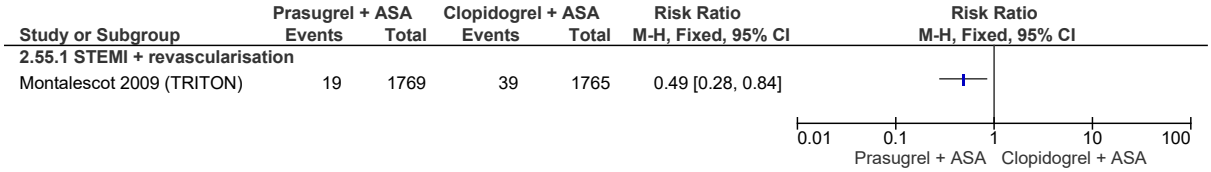


Figure 69: Stent thrombosis (type not specified) at 30 days

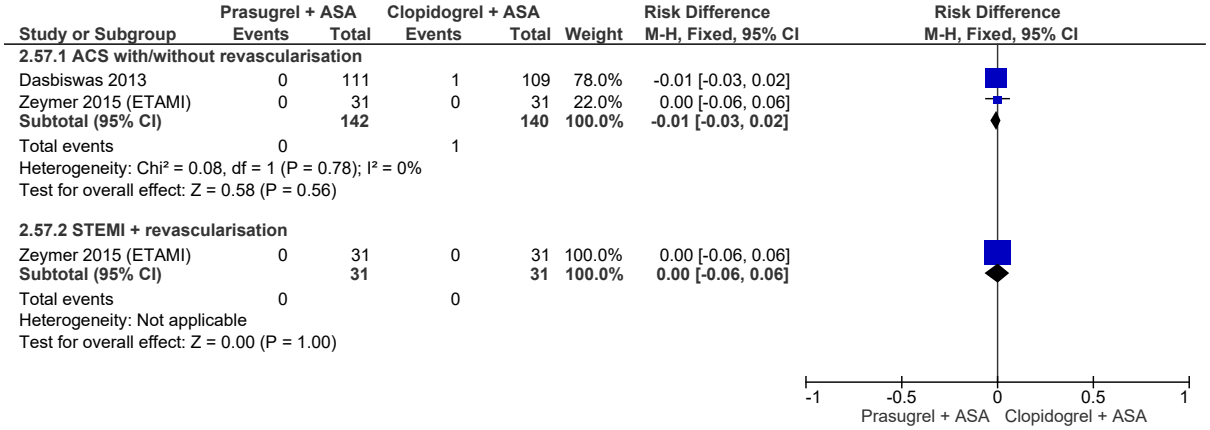


Figure 70: Stent thrombosis (probable or definite) at 1 year

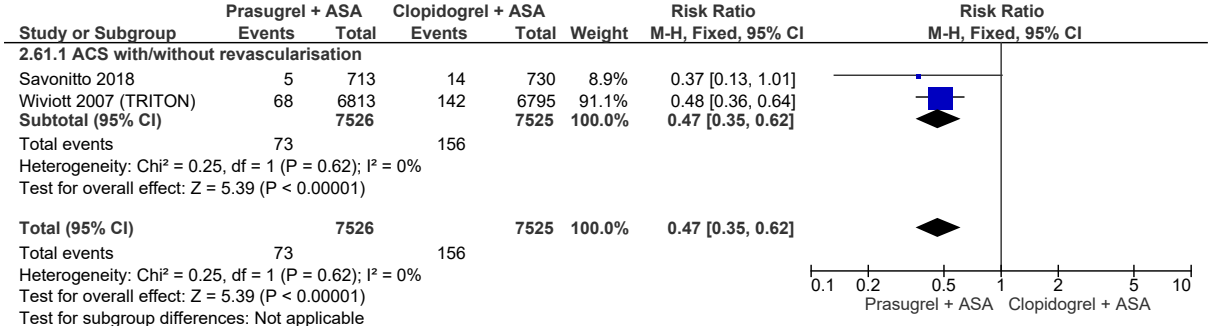


Figure 71: Other adverse effects at 30 days

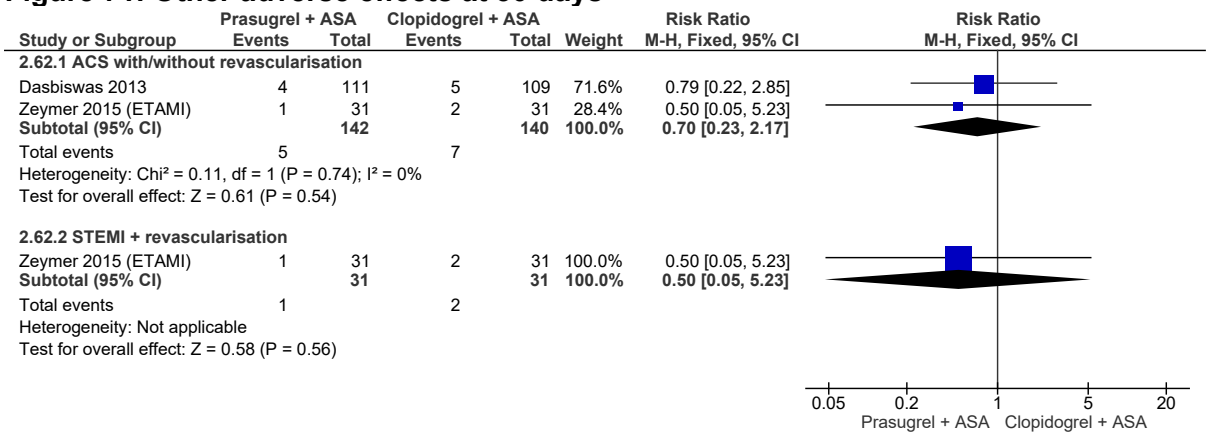


Figure 72: Other adverse effects at 1 year

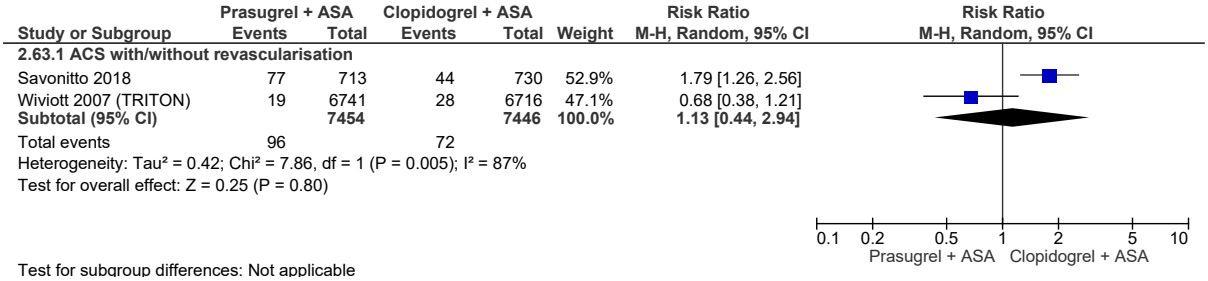


Figure 73: Unplanned urgent readmission at 30 days

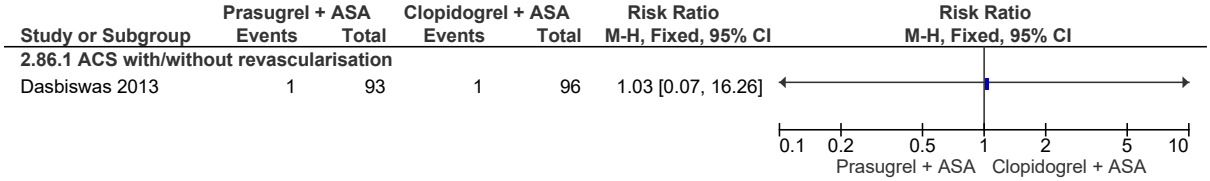
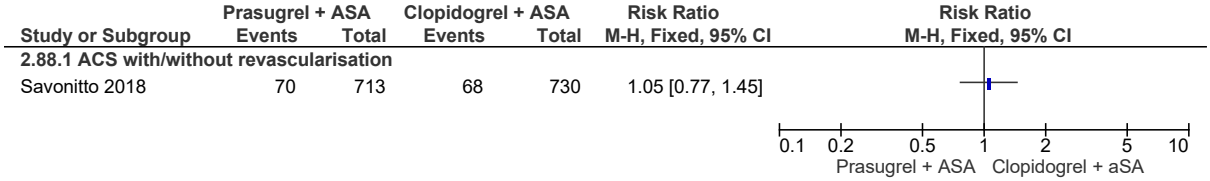


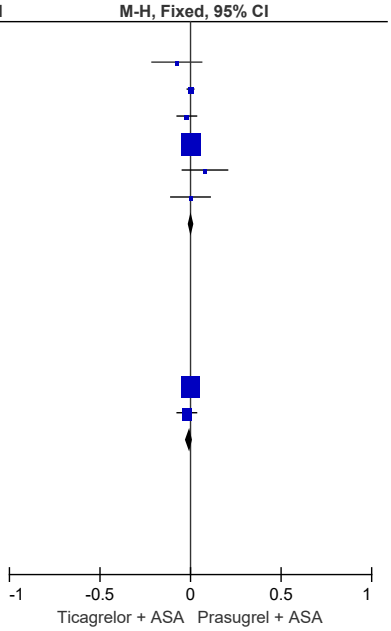
Figure 74: Unplanned urgent readmission at 1 year



E.3 Ticagrelor + ASA versus prasugrel + ASA

Figure 75: All-cause mortality at 30 days (ACS with/without revascularisation and UA/NSTEMI + revascularisation)

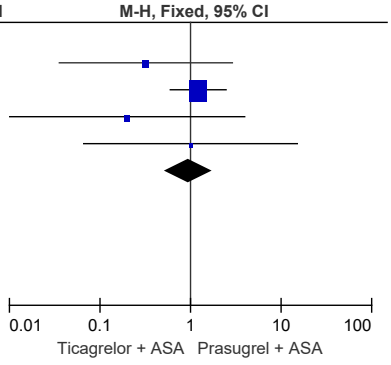
Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
3.21.1 ACS with/without revascularisation						
Alexopoulos 2012	1	28	3	27	3.2%	-0.08 [-0.21, 0.06]
Bonello 2015	0	106	0	107	12.6%	0.00 [-0.02, 0.02]
Laine 2014	0	50	1	50	5.9%	-0.02 [-0.07, 0.03]
Motovska 2016 (PRAGUE-18)	16	596	14	634	72.4%	0.00 [-0.01, 0.02]
Parodi 2013 (RAPID)	2	25	0	25	2.9%	0.08 [-0.05, 0.21]
Parodi 2014 (RAPID II)	1	25	1	25	2.9%	0.00 [-0.11, 0.11]
Subtotal (95% CI)		**830**		**868**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	20		19			
Heterogeneity: Chi² = 3.52, df = 5 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
3.21.3 UA/NSTEMI + revascularisation						
Bonello 2015	0	106	0	107	68.1%	0.00 [-0.02, 0.02]
Laine 2014	0	50	1	50	31.9%	-0.02 [-0.07, 0.03]
Subtotal (95% CI)		**156**		**157**	**100.0%**	**-0.01 [-0.03, 0.02]**
Total events	0		1			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						



Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%

Figure 76: All-cause mortality at 30 days (STEMI + revascularisation)

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.2 STEMI + revascularisation						
Alexopoulos 2012	1	28	3	27	15.2%	0.32 [0.04, 2.90]
Motovska 2016 (PRAGUE-18)	16	596	14	634	67.4%	1.22 [0.60, 2.47]
Parodi 2013 (RAPID)	0	25	2	25	12.4%	0.20 [0.01, 3.97]
Parodi 2014 (RAPID II)	1	25	1	25	5.0%	1.00 [0.07, 15.12]
Subtotal (95% CI)		**674**		**711**	**100.0%**	**0.94 [0.51, 1.75]**
Total events	18		20			
Heterogeneity: Chi² = 2.45, df = 3 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						



Test for subgroup differences: Not applicable

Figure 77: All-cause mortality at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Schupke 2019 (ISAR-REACT 5)	90	2012	73	2006	1.23 [0.91, 1.66]

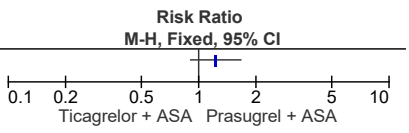


Figure 78: Cardiac mortality at 30 days (ACS with/without revascularisation and UA/NSTEMI + revascularisation)

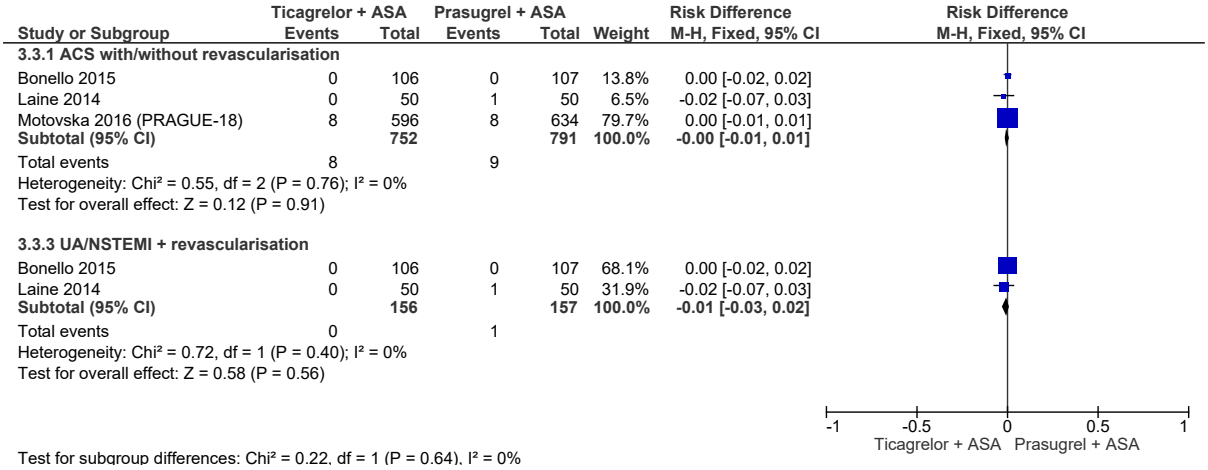


Figure 79: Cardiac mortality at 30 days (STEMI + revascularisation)

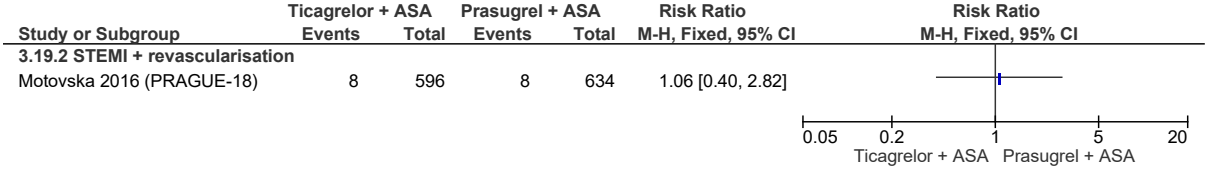


Figure 80: Cardiac mortality at 1 year

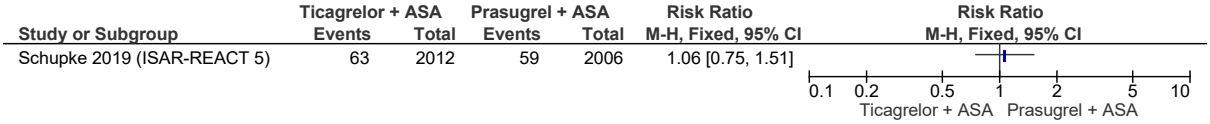


Figure 81: Re-infarction at 30 days (ACS with/without revascularisation and STEMI + revascularisation)

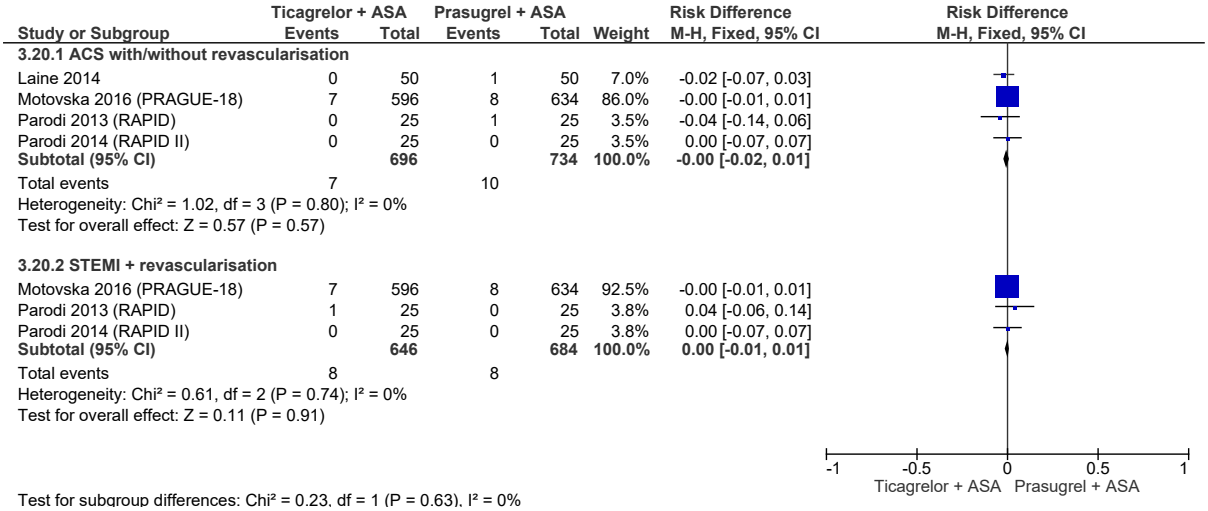


Figure 82: Re-infarction at 30 days (UA/NSTEMI + revascularisation)

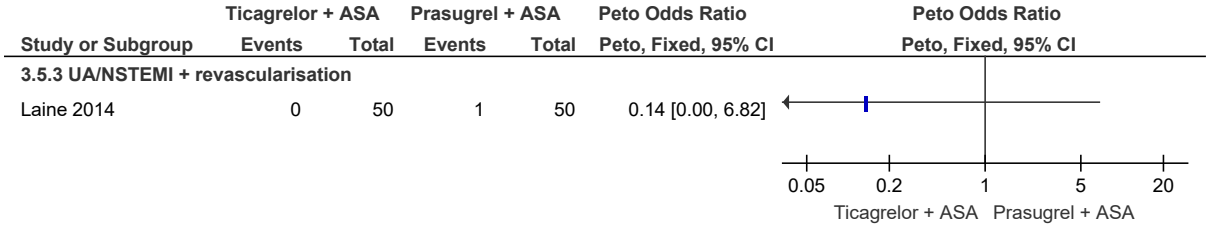


Figure 83: Re-infarction at 1 year

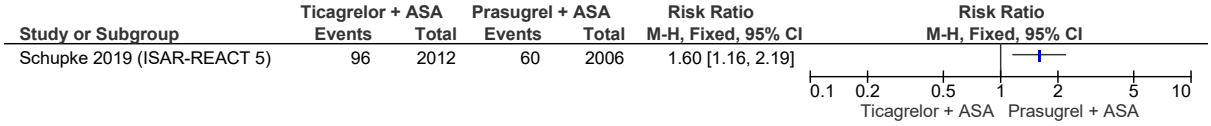


Figure 84: Major bleeding at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
3.7.1 ACS with/without revascularisation						
Alexopoulos 2012	0	28	0	27	3.2%	0.00 [-0.07, 0.07]
Bonello 2015	7	106	8	107	12.6%	-0.01 [-0.08, 0.06]
Laine 2014	0	50	0	50	5.9%	0.00 [-0.04, 0.04]
Motovska 2016 (PRAGUE-18)	2	596	4	634	72.4%	-0.00 [-0.01, 0.00]
Parodi 2013 (RAPID)	0	25	0	25	2.9%	0.00 [-0.07, 0.07]
Parodi 2014 (RAPID II)	1	25	2	25	2.9%	-0.04 [-0.17, 0.09]
Subtotal (95% CI)		**830**		**868**	**100.0%**	**-0.00 [-0.02, 0.01]**
Total events	10		14			
Heterogeneity: Chi² = 0.52, df = 5 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
3.7.2 STEMI + revascularisation						
Alexopoulos 2012	0	28	0	27	4.0%	0.00 [-0.07, 0.07]
Motovska 2016 (PRAGUE-18)	2	596	4	634	88.8%	-0.00 [-0.01, 0.00]
Parodi 2013 (RAPID)	0	25	0	25	3.6%	0.00 [-0.07, 0.07]
Parodi 2014 (RAPID II)	1	25	2	25	3.6%	-0.04 [-0.17, 0.09]
Subtotal (95% CI)		**674**		**711**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	3		6			
Heterogeneity: Chi² = 0.39, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
3.7.3 UA/NSTEMI + revascularisation						
Bonello 2015	7	106	8	107	68.1%	-0.01 [-0.08, 0.06]
Laine 2014	0	50	0	50	31.9%	0.00 [-0.04, 0.04]
Subtotal (95% CI)		**156**		**157**	**100.0%**	**-0.01 [-0.05, 0.04]**
Total events	7		8			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						

Test for subgroup differences: Chi² = 0.01, df = 2 (P = 1.00), I² = 0%

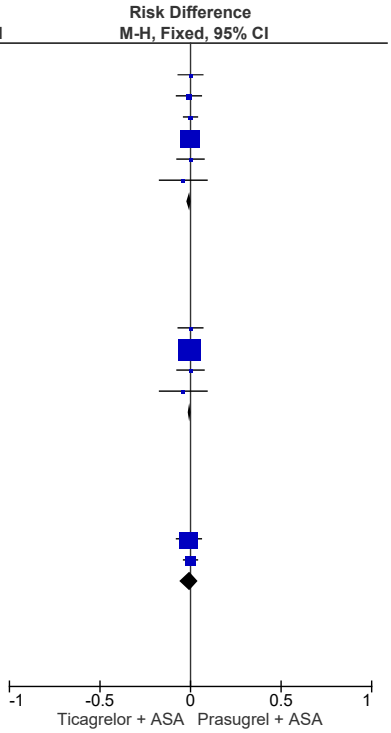


Figure 85: Major bleeding at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Schupke 2019 (ISAR-REACT 5)	95	1989	80	1773	1.06 [0.79, 1.42]

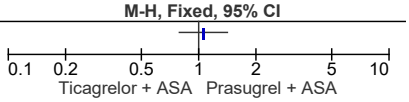


Figure 86: Minor bleeding at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.2 STEMI + revascularisation						
Alexopoulos 2012	3	28	1	27	4.0%	2.89 [0.32, 26.12]
Motovska 2016 (PRAGUE-18)	22	596	24	634	92.0%	0.98 [0.55, 1.72]
Parodi 2013 (RAPID)	3	25	0	25	2.0%	7.00 [0.38, 128.87]
Parodi 2014 (RAPID II)	2	25	0	25	2.0%	5.00 [0.25, 99.16]
Subtotal (95% CI)		**674**		**711**	**100.0%**	**1.25 [0.75, 2.09]**
Total events	30		25			
Heterogeneity: Chi² = 3.47, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Total (95% CI)		**674**		**711**	**100.0%**	**1.25 [0.75, 2.09]**
Total events	30		25			
Heterogeneity: Chi² = 3.47, df = 3 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Not applicable						

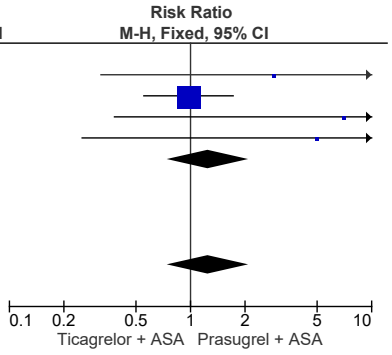


Figure 87: Stroke (type not specified) at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
3.11.1 ACS with/without revascularisation						
Bonello 2015	0	106	1	107	13.4%	-0.01 [-0.03, 0.02]
Laine 2014	0	50	0	50	6.3%	0.00 [-0.04, 0.04]
Motovska 2016 (PRAGUE-18)	1	596	2	634	77.2%	-0.00 [-0.01, 0.00]
Parodi 2014 (RAPID II)	0	25	0	25	3.1%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**777**		**816**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	1		3			
Heterogeneity: Chi² = 0.41, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
3.11.2 STEMI + revascularisation						
Motovska 2016 (PRAGUE-18)	1	596	2	634	96.1%	-0.00 [-0.01, 0.00]
Parodi 2014 (RAPID II)	0	25	0	25	3.9%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**621**		**659**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	1		2			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
3.11.3 UA/NSTEMI + revascularisation						
Bonello 2015	0	106	1	107	68.1%	-0.01 [-0.03, 0.02]
Laine 2014	0	50	0	50	31.9%	0.00 [-0.04, 0.04]
Subtotal (95% CI)		**156**		**157**	**100.0%**	**-0.01 [-0.03, 0.02]**
Total events	0		1			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						

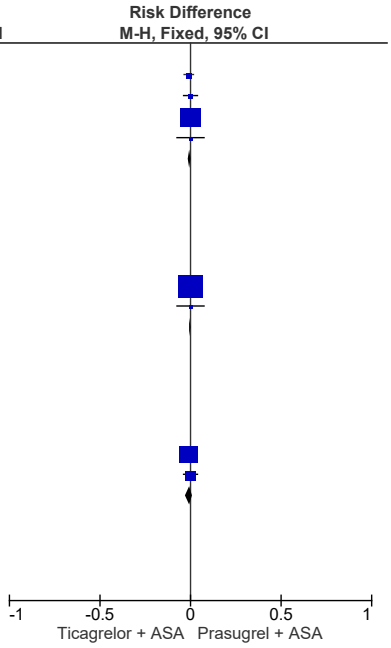


Figure 88: Stroke (any type) at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Schupke 2019 (ISAR-REACT 5)	22	2012	19	2006	1.15 [0.63, 2.13]

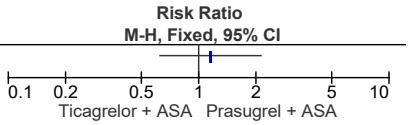


Figure 89: Need for revascularisation at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.15.1 STEMI + revascularisation					
Motovska 2016 (PRAGUE-18)	7	596	9	634	0.83 [0.31, 2.21]

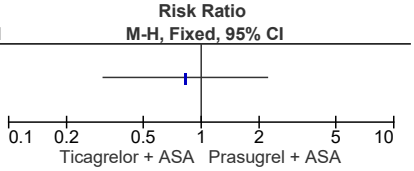


Figure 90: Stent thrombosis (definite) at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.13.2 STEMI + revascularisation					
Motovska 2016 (PRAGUE-18)	5	596	3	634	1.77 [0.43, 7.39]

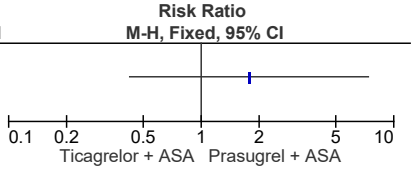


Figure 91: Stent thrombosis (type not specified) at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
3.14.2 STEMI + revascularisation						
Parodi 2013 (RAPID)	0	25	1	25	50.0%	-0.04 [-0.14, 0.06]
Parodi 2014 (RAPID II)	0	25	0	25	50.0%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**-0.02 [-0.09, 0.05]**
Total events	0		1			

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)

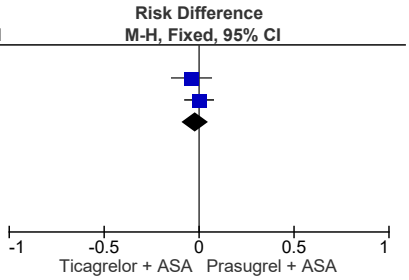


Figure 92: Stent thrombosis (definite or probable) at 1 year

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Risk Ratio M-H, Fixed, 95% CI
Schupke 2019 (ISAR-REACT 5)	26	2012	20	2006	1.30 [0.73, 2.31]

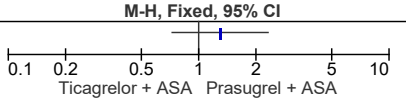


Figure 93: Breathing adverse effects at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
3.16.2 STEMI + revascularisation					
Parodi 2013 (RAPID)	5	25	0	25	8.83 [1.42, 54.99]

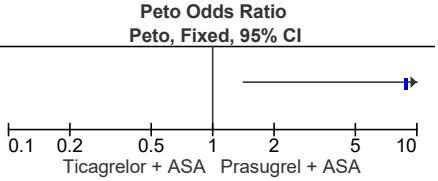


Figure 94: Bradycardic adverse effects at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
3.17.2 STEMI + revascularisation					
Parodi 2014 (RAPID)	1	25	0	25	7.39 [0.15, 372.38]

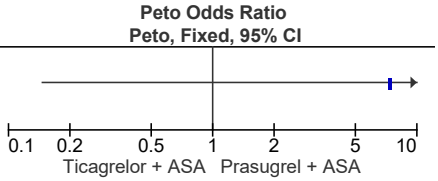
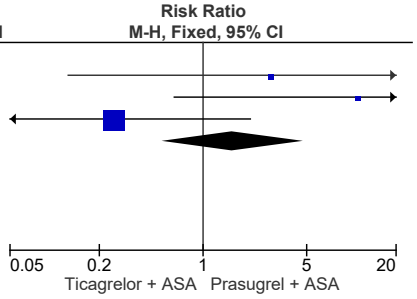


Figure 95: Other adverse effects at 30 days

Study or Subgroup	Ticagrelor + ASA Events	Total	Prasugrel + ASA Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.18.2 STEMI + revascularisation						
Lee 2015	1	20	0	19	10.2%	2.86 [0.12, 66.11]
Parodi 2013 (RAPID)	5	25	0	25	10.0%	11.00 [0.64, 188.95]
Parodi 2014 (RAPID II)	1	25	4	25	79.8%	0.25 [0.03, 2.08]
Subtotal (95% CI)		**70**		**69**	**100.0%**	**1.59 [0.53, 4.74]**
Total events	7		4			

Heterogeneity: Chi² = 4.84, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.83 (P = 0.41)

Test for subgroup differences: Not applicable



E.3.1 Minimal important differences for continuous outcomes

The MID values reported in Table 25, were used to assess imprecision for the various continuous outcomes included in this evidence review. Continous outcomes were only reported for the comparison: prasugrel versus clopidogrel.

Table 25: Minimal important difference: Prasgurel + aspirin versus clopidogrel + aspirin

Outcomes	Minimal important difference (MID)
Health-related quality of life (EQ5D) (people aged <75 years) at 1 year Scale: 0-100 (higher is better)	7.7
Health-related quality of life (SAQ Physical) (people aged <75 years) at 1 year Scale: 0-100 (higher is better)	11.6
Health-related quality of life (SF-12 Physical) (people aged <75 years) at 1 year Scale: 0-100 (higher is better)	5.4
Health-related quality of life (SF-12 Mental) (people aged <75 years) at 1 year Scale: 0-100 (higher is better)	5.2
Health-related quality of life (SF-36 Mental) (people aged <75 years) at 1 year Scale: 0-100 (higher is better)	5.5

Appendix F: GRADE tables

Table 26: Clinical evidence profile: ticagrelor + ASA versus clopidogrel + ASA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ticagrelor + ASA	clopidogrel + ASA	Relative (95% CI)	Absolute		
All-cause mortality - ACS with/without revascularisation (follow-up 30 days)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	190/9940 (1.9 %)	224/9872 (2.3 %)	see comment[6]	4 fewer per 1000 (from 7 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality - STEMI + revascularisation (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/320 (1.6%)	10/310 (3.2%)	RR 0.48 (0.17 to 1.39)	17 fewer per 1000 (from 27 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
(HR) All-cause mortality - UA/NSTEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.64 (0.44 to 0.93)	-[3]	⊕⊕OO LOW	CRITICAL
(HR) All-cause mortality - UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.84 (0.63 to 1.12)	-[3]	⊕⊕OO LOW	CRITICAL
All-cause mortality - ACS with/without revascularisation (follow-up 1 year)												

6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	425/10244 (4.1%)	543/10199 (5.3%)	RR 0.78 (0.69 to 0.88)	12 fewer per 1000 (from 6 fewer to 17 fewer)	⊕⊕OO LOW	CRITICAL
All-cause mortality - STEMI + revascularisation (follow-up 1 year)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	182/4102 (4.4%)	229/4140 (5.5%)	RR 0.8 (0.66 to 0.97)	11 fewer per 1000 (from 2 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
(HR) All-cause mortality - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.75 (0.53 to 1.06)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) All-cause mortality - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.73 (0.57 to 0.93)	-[3]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/575 (1.7%)	9/568 (1.6%)	RR 1.1 (0.45 to 2.69)	2 more per 1000 (from 9 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
Cardiac mortality - STEMI + revascularisation (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/241 (1.7%)	7/241 (2.9%)	RR 0.57 (0.17 to 1.92)	12 fewer per 1000 (from 24 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL
(HR) Cardiac mortality - UA/NSTEMI + revascularisation (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.67 (0.43 to 1.04)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Cardiac mortality - UA/NSTEMI + no revascularisation (follow-up 30 days)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.84 (0.62 to 1.14)	-[3]	⊕OOO VERY LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 1 year)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	374/10319 (3.6%)	479/10392 (4.6%)	RR 0.78 (0.69 to 0.89)	10 fewer per 1000 (from 5 fewer to 14 fewer)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - STEMI + revascularisation (follow-up 1 year)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	165/4237 (3.9%)	210/4393 (4.8%)	RR 0.81 (0.66 to 0.98)	9 fewer per 1000 (from 1 fewer to 16 fewer)	⊕⊕OO LOW	CRITICAL
(HR) Cardiac mortality - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.76 (0.52 to 1.11)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Cardiac mortality - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.75 (0.58 to 0.97)	-[3]	⊕OOO VERY LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 30 days)												
6	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	134/9942 (1.3%)	193/9876 (2%)	RR 0.69 (0.56 to 0.86)	6 fewer per 1000 (from 3 fewer to 9 fewer)	⊕⊕OO LOW	CRITICAL
Re-infarction - STEMI + revascularisation (follow-up 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/373 (1.6%)	17/363 (4.7%)	RR 0.37 (0.15 to 0.89)	30 fewer per 1000 (from 5 fewer to 40 fewer)	⊕⊕OO LOW	CRITICAL
(HR) Re-infarction - UA/NSTEMI + revascularisation (follow-up 30 days)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.86 (0.63 to 1.17)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Re-infarction - UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.89 (0.68 to 1.16)	-[3]	⊕OOO VERY LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 1 year)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	541/10529 (5.1%)	651/10600 (6.1%)	RR 0.83 (0.74 to 0.93)	10 fewer per 1000 (from 4 fewer to 16 fewer)	⊕⊕OO LOW	CRITICAL
Re-infarction - STEMI + revascularisation (follow-up 1 year)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	163/4387 (3.7%)	223/4541 (4.9%)	RR 0.75 (0.61 to 0.91)	12 fewer per 1000 (from 4 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
(HR) Re-infarction - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.90 (0.68 to 1.19)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Re-infarction - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 0.94 (0.75 to 1.18)	-[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding - ACS with/without revascularisation (follow-up 30 days)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	675/9949 (6.8%)	669/9883 (6.8%)	see comment[6]	0 fewer per 1000 (from 7 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding - STEMI + revascularisation (follow-up 30 days)												

4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/380 (1.8%)	5/370 (1.4%)	see comment[6]	5 more per 1000 (from 8 fewer to 43 more)	⊕OOO VERY LOW	CRITICAL
(HR) Major bleeding - UA/NSTEMI + revascularisation (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.14 (0.84 to 1.56)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Major bleeding - UA/NSTEMI + no revascularisation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.18 (0.91 to 1.53)	-[3]	⊕OOO VERY LOW	CRITICAL
Major bleeding - ACS with/without revascularisation (follow-up 1 year)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1011/10157 (10%)	968/10049 (9.6%)	RR 1.04 (0.96 to 1.13)	4 more per 1000 (from 4 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Major bleeding - STEMI + revascularisation (follow-up 1 year)												
3	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	308/4230 (7.3%)	321/4203 (7.6%)	RR 0.96 (0.83 to 1.12)	2 fewer per 1000 (from 13 fewer to 9 more)	⊕⊕OO LOW	CRITICAL
(HR) Major bleeding - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.10 (0.84 to 1.44)	-[3]	⊕OOO VERY LOW	CRITICAL
(HR) Major bleeding - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.05 (0.88 to 1.25)	-[3]	⊕OOO VERY LOW	CRITICAL
Minor bleeding - ACS with/without revascularisation (follow-up 30 days)												

6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61/765 (8%)	40/746 (5.4%)	RR 1.49 (1.02 to 2.16)	26 more per 1000 (from 1 more to 62 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding - STEMI + revascularisation (follow-up 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/380 (13.2%)	36/370 (9.7%)	RR 1.36 (0.91 to 2.02)	35 more per 1000 (from 9 fewer to 99 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding - ACS with/without revascularisation (follow-up 1 year)												
6	randomised trials	serious[1]	serious[4]	no serious indirectness	serious[2]	none	498/10157 (4.9%)	382/10227 (3.7%)	RR 1.34 (1.18 to 1.53)	13 more per 1000 (from 7 more to 20 more)	⊕OOO VERY LOW	CRITICAL
Minor bleeding - STEMI + revascularisation (follow-up 1 year)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	198/4080 (4.9%)	158/4233 (3.7%)	RR 1.37 (1.12 to 1.68)	14 more per 1000 (from 4 more to 25 more)	⊕⊕OO LOW	CRITICAL
Bleeding (type not specified) – UA/NSTEMI with revascularisation at 1 year (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/124 (11.3%)	4/120 (3.3%)	RR 3.39 (1.15 to 10)	80 more per 1000 (from 5 more to 300 more)	⊕⊕OO LOW	CRITICAL
Stroke (type not specified) - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	61/9732 (0.63%)	46/9668 (0.48%)	see comment[6]	2 more per 1000 (from 0 fewer to 4 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	2/163 (1.2%)	2/155 (1.3%)	see comment[6]	0 fewer per 1000 (from 11 fewer to 77 more)	⊕OOO VERY LOW	IMPORTANT

(HR) Stroke (type not specified) - UA/NSTEMI + revascularisation (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 1.14 (0.54 to 2.41)	-[3]	⊕OOO VERY LOW	IMPORTANT
(HR) Stroke (type not specified) - UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.84 (0.50 to 1.41)	-[3]	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - ACS with/without revascularisation (follow-up 1 year)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/10319 (1.4%)	127/10392 (1.2%)	RR 1.13 (0.89 to 1.43)	2 more per 1000 (from 1 fewer to 5 more)	⊕⊕⊕O MODERATE	IMPORTANT
Stroke (type not specified) - STEMI + revascularisation (follow-up 1 year)												
4	randomised trials	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	59/4237 (1.4%)	47/4393 (1.1%)	RR 1.29 (0.88 to 1.9)	3 more per 1000 (from 1 fewer to 10 more)	⊕⊕OO LOW	IMPORTANT
(HR) Stroke (type not specified) - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 1.18 (0.60 to 2.32)	-[3]	⊕OOO VERY LOW	IMPORTANT
(HR) Stroke (type not specified) - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.92 (0.58 to 1.46)	-[3]	⊕OOO VERY LOW	IMPORTANT
Need for revascularisation - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/226 (0.88%)	8/216 (3.7%)	Peto OR 0.29 (0.08 to 1)	26 fewer per 1000 (from 34 fewer to 0 more)	⊕⊕OO LOW	IMPORTANT

Need for revascularisation - ACS with/without revascularisation (follow-up 1 year)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/571 (1.9%)	47/689 (6.8%)	RR 0.31 (0.16 to 0.6)	47 fewer per 1000 (from 27 fewer to 57 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Need for revascularisation - STEMI + revascularisation (follow-up 1 year)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/511 (1.6%)	42/629 (6.7%)	RR 0.27 (0.13 to 0.57)	49 fewer per 1000 (from 29 fewer to 58 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Stent thrombosis (type not specified) - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/87 (0%)	4/87 (4.6%)	Peto OR 0.13 (0.02 to 0.94)	40 fewer per 1000 (from 3 fewer to 45 fewer)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (probable or definite) - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	118/5640 (2.1%)	158/5649 (2.8%)	RR 0.75 (0.59 to 0.95)	7 fewer per 1000 (from 1 fewer to 11 fewer)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (probable or definite) - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73/3752 (1.9%)	101/3792 (2.7%)	RR 0.73 (0.54 to 0.98)	7 fewer per 1000 (from 1 fewer to 12 fewer)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (type not specified)- ACS with/without revascularisation (follow-up 1 year)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	0/485 (0%)	7/601 (1.2%)	see comment[6]	10 fewer per 1000 (from 3 fewer to 11 fewer)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (type not specified) - STEMI + revascularisation (follow-up 1 year)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/324 (0%)	3/320 (0.94%)	see comment[6]	8 fewer per 1000 (from 9 fewer to 16 more)	⊕OOO VERY LOW	IMPORTANT
Stent thrombosis (type not specified) - NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/161 (0%)	4/281 (1.4%)	Peto OR 0.21 (0.03 to 1.58)	11 fewer per 1000 (from 14 fewer to 8 more)	⊕OOO VERY LOW	IMPORTANT
Breathing adverse effects - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/163 (12.3%)	8/155 (5.2%)	RR 2.39 (1.09 to 5.27)	72 more per 1000 (from 5 more to 220 more)	⊕⊕OO LOW	IMPORTANT
Breathing adverse effects - ACS with/without revascularisation (follow-up 1 year)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1292/9636 (13.4%)	730/9586 (7.6%)	RR 1.76 (1.62 to 1.92)	58 more per 1000 (from 47 more to 70 more)	⊕⊕⊕O MODERATE	IMPORTANT
Breathing adverse effects - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	468/3719 (12.6%)	314/3752 (8.4%)	RR 1.5 (1.31 to 1.72)	42 more per 1000 (from 26 more to 60 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bradycardic adverse effects - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31/1148 (2.7%)	23/1161 (2%)	RR 1.36 (0.8 to 2.29)	7 more per 1000 (from 4 fewer to 26 more)	⊕OOO VERY LOW	IMPORTANT
Bradycardic adverse effects - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/163 (6.1%)	6/155 (3.9%)	RR 1.6 (0.62 to 4.1)	23 more per 1000 (from 15 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT

Bradycardic adverse effects - ACS with/without revascularisation (follow-up 1 year)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	503/9760 (5.2%)	460/9706 (4.7%)	RR 1.09 (0.96 to 1.23)	4 more per 1000 (from 2 fewer to 11 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bradycardic adverse effects - STEMI + revascularisation (follow-up 1 year)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	224/3843 (5.8%)	217/3872 (5.6%)	RR 1.04 (0.87 to 1.25)	2 more per 1000 (from 7 fewer to 14 more)	⊕⊕OO LOW	IMPORTANT
Other adverse effects - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/214 (21%)	34/204 (16.7%)	RR 1.26 (0.85 to 1.88)	43 more per 1000 (from 25 fewer to 147 more)	⊕⊕OO LOW	IMPORTANT
Other adverse effects - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/163 (18.4%)	25/155 (16.1%)	RR 1.14 (0.7 to 1.85)	23 more per 1000 (from 48 fewer to 137 more)	⊕OOO VERY LOW	IMPORTANT
Other adverse effects - ACS with/without revascularisation (follow-up 1 year)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	499/9696 (5.1%)	487/9646 (5%)	RR 1.02 (0.94 to 1.11)	1 more per 1000 (from 3 fewer to 6 more)	⊕⊕⊕O MODERATE	IMPORTANT
Other adverse effects - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77/3719 (2.1%)	62/3752 (1.7%)	RR 1.25 (0.9 to 1.75)	4 more per 1000 (from 2 fewer to 12 more)	⊕⊕OO LOW	IMPORTANT
Unplanned urgent readmission (rehospitalisation) - STEMI + revascularisation (follow-up 30 days)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/76 (2.6%)	4/68 (5.9%)	RR 0.45 (0.08 to 2.37)	32 fewer per 1000 (from 54 fewer to 81 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Absolute effects could not be calculated as event rates were not reported
[4] Downgraded by 1 because of heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis

[5] Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision

[6] No relative effect due to 0 events. Risk difference calculated in Review Manager

Table 27: Clinical evidence profile: prasugrel + ASA versus clopidogrel + ASA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prasugrel + ASA**	**clopidogrel + ASA**	**Relative (95% CI)**	**Absolute**		
All-cause mortality - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	70/6574 (1.1%)	91/6568 (1.4%)	RR 0.77 (0.56 to 1.05)	3 fewer per 1000 (from 6 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	29/1800 (1.6%)	46/1796 (2.6%)	RR 0.63 (0.40 to 1.00)	9 fewer per 1000 (from 15 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality – UA/NSTEMI + no revascularisation (follow-up 30 days)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	39/4663 (0.84%)	44/4663 (0.94%)	RR 0.89 (0.58 to 1.36)	1 fewer per 1000 (from 4 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - ACS with/without revascularisation (follow-up 1 year)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	226/7564 (3%)	226/7562 (3%)	RR 1 (0.83 to 1.2)	0 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	58/1769 (3.3%)	76/1765 (4.3%)	RR 0.76 (0.54 to 1.06)	10 fewer per 1000 (from 20 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	60/6525 (0.92%)	80/6524 (1.2%)	RR 0.75 (0.54 to 1.05)	3 fewer per 1000 (from 6 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	25/1769 (1.4%)	41/1765 (2.3%)	RR 0.61 (0.37 to 1)	9 fewer per 1000 (from 15 fewer to 0 more)	⊕⊕OO LOW	IMPORTANT
Cardiac mortality – UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	35/4663 (0.75%)	38/4663 (0.81%)	RR 0.92 (0.58 to 1.46)	1 fewer per 1000 (from 3 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 1 year)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	159/7526 (2.1%)	181/7525 (2.4%)	RR 0.88 (0.71 to 1.09)	3 fewer per 1000 (from 7 fewer to 2 more)	⊕⊕OO LOW	CRITICAL

Cardiac mortality - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	43/1769 (2.4%)	58/1765 (3.3%)	RR 0.74 (0.5 to 1.09)	9 fewer per 1000 (from 16 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	90/5044 (1.8%)	92/5030 (1.8%)	RR 0.98 (0.73 to 1.3)	0 fewer per 1000 (from 5 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
(HR) Cardiac mortality - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 1.00 (0.78 to 1.28)	-[3]	⊕OOO VERY LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	161/6556 (2.5%)	201/6555 (3.1%)	see comment[8]	6 fewer per 1000 (from 1 fewer to 11 fewer)	⊕OOO VERY LOW	CRITICAL
Re-infarction - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	87/1800 (4.8%)	123/1796 (6.8%)	see comment[8]	20 fewer per 1000 (from 5 fewer to 32 fewer)	⊕⊕OO LOW	CRITICAL
Re-infarction – UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	74/4663 (1.6%)	78/4663 (1.7%)	RR 0.95 (0.69 to 1.3)	1 fewer per 1000 (from 5 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 1 year)												

3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	499/7526 (6.6%)	652/7525 (8.7%)	RR 0.76 (0.68 to 0.85)	21 fewer per 1000 (from 13 fewer to 28 fewer)	⊕⊕OO LOW	CRITICAL
Re-infarction - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	119/1769 (6.7%)	157/1765 (8.9%)	RR 0.76 (0.6 to 0.95)	21 fewer per 1000 (from 4 fewer to 36 fewer)	⊕⊕OO LOW	CRITICAL
Re-infarction - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	366/5044 (7.3%)	476/5030 (9.5%)	RR 0.77 (0.67 to 0.87)	22 fewer per 1000 (from 12 fewer to 31 fewer)	⊕⊕OO LOW	CRITICAL
(HR) Re-infarction - UA/NSTEMI + no revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	HR 0.97 (0.7 to 1.21)	-[3]	⊕⊕OO LOW	CRITICAL
Major bleeding - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	24/6503 (0.37%)	29/6491 (0.45%)	see comment[8]	1 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	17/1769 (0.96%)	23/1765 (1.3%)	RR 0.74 (0.4 to 1.38)	3 fewer per 1000 (from 8 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding – UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/4623 (0.15%)	6/4617 (0.13%)	RR 1.17 (0.39 to 3.46)	0 more per 1000 (from 1 fewer to 3 more)	⊕⊕OO LOW	CRITICAL

Bleeding (major and minor) - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/31 (3.2%)	0/31 (0%)	Peto OR 7.39 (0.15 to 372.38)	-	⊕⊕OO LOW	CRITICAL
Major bleeding - ACS with/without revascularisation (follow-up 1 year)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	183/7454 (2.5%)	129/7446 (1.7%)	RR 1.42 (1.13 to 1.77)	7 more per 1000 (from 2 more to 13 more)	⊕⊕OO LOW	CRITICAL
Major bleeding - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	38/1769 (2.1%)	34/1765 (1.9%)	RR 1.12 (0.71 to 1.76)	2 more per 1000 (from 6 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	108/5001 (2.2%)	77/4980 (1.5%)	RR 1.4 (1.05 to 1.87)	6 more per 1000 (from 1 more to 13 more)	⊕⊕OO LOW	CRITICAL
Minor bleeding - ACS with/without revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	serious[4]	no serious indirectness	serious[1]	none	40/1880 (2.1%)	58/1874 (3.1%)	RR 0.69 (0.46 to 1.02)	10 fewer per 1000 (from 17 fewer to 1 more)	⊕OOO VERY LOW	CRITICAL
Minor bleeding - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	35/1769 (2%)	57/1765 (3.2%)	RR 0.61 (0.4 to 0.93)	13 fewer per 1000 (from 2 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
Minor bleeding - ACS with/without revascularisation (follow-up 1 year)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	16/713 (2.2%)	8/730 (1.1%)	RR 2.05 (0.88 to 4.75)	12 more per 1000 (from 1 fewer to 41 more)	⊕⊕OO LOW	CRITICAL
Health-related quality of life - UA/NSTEMI + no revascularisation (follow-up 1 year; measured with: EQ5D; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2888	2876	-	MD 1 higher (0.22 to 1.78 higher)	⊕⊕⊕O MODERATE	CRITICAL
Health-related quality of life - UA/NSTEMI + no revascularisation (follow-up 1 year; measured with: SAQ Physical; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	891	883	-	MD 1 higher (1.17 lower to 3.17 higher)	⊕⊕⊕O MODERATE	CRITICAL
Health-related quality of life - UA/NSTEMI + no revascularisation (follow-up 1 year; measured with: SF-12 Physical; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	891	883	-	MD 0.3 higher (0.7 lower to 1.3 higher)	⊕⊕⊕O MODERATE	CRITICAL
Health-related quality of life - UA/NSTEMI + no revascularisation (follow-up 1 year; measured with: SF-12 Mental; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	891	883	-	MD 0 higher (0.97 lower to 0.97 higher)	⊕⊕⊕O MODERATE	CRITICAL
Health-related quality of life - UA/NSTEMI + no revascularisation (follow-up 1 year; measured with: SF-36; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	891	883	-	MD 0.4 higher (0.64 lower to 1.44 higher)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (type not specified) - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	20/6525 (0.31%)	28/6524 (0.43%)	RR 0.71 (0.4 to 1.27)	1 fewer per 1000 (from 3 fewer to 1 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - STEMI + revascularisation (follow-up 30 days)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	7/1769 (0.4%)	16/1765 (0.91%)	RR 0.44 (0.18 to 1.06)	5 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕OO LOW	IMPORTANT
Stroke (type not specified) – UA/NSTEMI + no revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/4663 (0.26%)	11/4663 (0.24%)	RR 1.09 (0.48 to 2.47)	0 more per 1000 (from 1 fewer to 3 more)	⊕⊕OO LOW	IMPORTANT
Stroke (type not specified) - ACS with/without revascularisation (follow-up 1 year)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	69/7564 (0.91%)	74/7562 (0.98%)	RR 0.93 (0.67 to 1.29)	1 fewer per 1000 (from 3 fewer to 3 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	26/1769 (1.5%)	25/1765 (1.4%)	RR 1.04 (0.6 to 1.79)	1 more per 1000 (from 6 fewer to 11 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - UA/NSTEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	49/5044 (0.97%)	46/5030 (0.91%)	RR 1.06 (0.71 to 1.59)	1 more per 1000 (from 3 fewer to 5 more)	⊕OOO VERY LOW	IMPORTANT
(HR) Stroke (type not specified) in people aged <75 years - (UA/NSTEMI + no revascularisation) (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 0.86 (0.50 to 1.48)	-[3]	⊕OOO VERY LOW	IMPORTANT
Need for revascularisation - ACS with/without revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	22/1862 (1.2%)	33/1861 (1.8%)	see comment[8]	6 fewer per 1000 (from 11 fewer to 2 more)	⊕OOO VERY LOW	IMPORTANT

Need for revascularisation - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	22/1769 (1.2%)	33/1765 (1.9%)	RR 0.67 (0.39 to 1.14)	6 fewer per 1000 (from 11 fewer to 3 more)	⊕⊕OO LOW	IMPORTANT
Need for revascularisation - ACS with/without revascularisation (follow-up 1 year)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	158/6851 (2.3%)	235/6832 (3.4%)	RR 0.67 (0.55 to 0.82)	11 fewer per 1000 (from 6 fewer to 15 fewer)	⊕⊕OO LOW	IMPORTANT
Need for revascularisation - STEMI + revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	38/1769 (2.1%)	54/1765 (3.1%)	RR 0.7 (0.47 to 1.06)	9 fewer per 1000 (from 16 fewer to 2 more)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (definite or probable) - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	19/1769 (1.1%)	39/1765 (2.2%)	RR 0.49 (0.28 to 0.84)	11 fewer per 1000 (from 4 fewer to 16 fewer)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (type not specified) - ACS with/without revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/142 (0%)	1/140 (0.71%)	see comment[8]	5 fewer per 1000 (from 7 fewer to 50 more)	⊕OOO VERY LOW	IMPORTANT
Stent thrombosis (type not specified) - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/31 (0%)	0/31 (0%)	-[5]	-[5]	⊕OOO VERY LOW	IMPORTANT
Stent thrombosis (definite or probable) - ACS with/without revascularisation (follow-up 1 year)												

2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/7526 (0.97%)	156/7525 (2.1%)	RR 0.47 (0.35 to 0.62)	11 fewer per 1000 (from 8 fewer to 13 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Other adverse effects - ACS with/without revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/142 (3.5%)	7/140 (5%)	RR 0.7 (0.23 to 2.17)	15 fewer per 1000 (from 38 fewer to 59 more)	⊕OOO VERY LOW	IMPORTANT
Other adverse effects - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/31 (3.2%)	2/31 (6.5%)	RR 0.5 (0.05 to 5.23)	32 fewer per 1000 (from 61 fewer to 273 more)	⊕⊕OO LOW	IMPORTANT
Other adverse effects - ACS with/without revascularisation (follow-up 1 year)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	96/7454 (1.3%)	72/7446 (0.97%)	RR 1.13 (0.44 to 2.94)	1 more per 1000 (from 5 fewer to 19 more)	⊕OOO VERY LOW	IMPORTANT
Unplanned urgent readmission - ACS with/without revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/93 (1.1%)	1/96 (1%)	RR 1.03 (0.07 to 16.26)	0 more per 1000 (from 10 fewer to 159 more)	⊕OOO VERY LOW	IMPORTANT
Unplanned urgent readmission - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	70/713 (9.8%)	68/730 (9.3%)	RR 1.05 (0.77 to 1.45)	5 more per 1000 (from 21 fewer to 42 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Absolute effects could not be calculated as event rates were not reported
[4] Downgraded by 1 because of heterogeneity, I2= > 50%, p= > 0.04, unexplained by subgroup analysis
[5] Zero events in both arms. Relative risk and absolute effects could not be calculated.
[6] Absolute effects could not be calculated due to zero events in one of the arms

[7] Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision

[8] No relative effect due to 0 events. Risk difference calculated in Review Manager

Table 28: Clinical evidence profile: ticagrelor + ASA versus prasugrel + ASA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ticagrelor + ASA	prasugrel + ASA	Relative (95% CI)	Absolute		
All-cause mortality - ACS with/without revascularisation (follow-up 30 days)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	20/830 (2.4%)	19/868 (2.2%)	see comment[5]	2 more per 1000 (from 9 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - STEMI + revascularisation (follow-up 30 days)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18/674 (2.7%)	20/711 (2.8%)	RR 0.94 (0.51 to 1.75)	2 fewer per 1000 (from 14 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality - UA/NSTEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/156 (0%)	1/157 (0.64%)	see comment[5]	4 fewer per 1000 (from 6 fewer to 45 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious	none	90/2012 (4.5%)	73/2006 (3.6%)	RR 1.23 (0.91 to 1.66)	8 more per 1000 (from 4 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 30 days)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	8/752 (1.1%)	9/791 (1.1%)	see comment[5]	1 fewer per 1000 (from 7 fewer to 16 more)	⊕⊕OO LOW	CRITICAL

Cardiac mortality - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/596 (1.3%)	8/634 (1.3%)	RR 1.06 (0.4 to 2.82)	1 more per 1000 (from 8 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - UA/NSTEMI + revascularisation (follow-up 30 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/156 (0%)	1/157 (0.64%)	see comment[5]	4 fewer per 1000 (from 6 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
Cardiac mortality - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	63/2012 (3.1%)	59/2006 (2.9%)	RR 1.06 (0.75 to 1.51)	2 more per 1000 (from 7 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/696 (1%)	10/734 (1.4%)	see comment[5]	3 fewer per 1000 (from 9 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Re-infarction - STEMI + revascularisation (follow-up 30 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/646 (1.2%)	8/684 (1.2%)	see comment[5]	1 more per 1000 (from 7 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Re-infarction - UA/NSTEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/50 (0%)	1/50 (2%)	Peto 0.14 (0.00 to 6.82)	17 fewer per 1000 (from 20 fewer to 102 more)	⊕⊕OO LOW	CRITICAL
Re-infarction - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	96/2012 (4.8%)	60/2006 (3%)	RR 1.6 (1.16 to 2.19)	18 more per 1000 (from 5 more to 36 more)	⊕⊕OO LOW	CRITICAL

Major bleeding - ACS with/without revascularisation (follow-up 30 days)												
6	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	10/830 (1.2%)	14/868 (1.6%)	see comment[5]	4 fewer per 1000 (from 11 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding - STEMI + revascularisation (follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/674 (0.45%)	6/711 (0.84%)	see comment[5]	4 fewer per 1000 (from 7 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding - UA/NSTEMI + revascularisation (follow-up 30 days)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/156 (4.5%)	8/157 (5.1%)	see comment[5]	6 fewer per 1000 (from 34 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Major bleeding - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	95/1989 (4.8%)	80/1773 (4.5%)	RR 1.06 (0.79 to 1.42)	3 more per 1000 (from 9 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Minor bleeding - STEMI + revascularisation (follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	30/674 (4.5%)	25/711 (3.5%)	RR 1.25 (0.75 to 2.09)	9 more per 1000 (from 9 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Stroke (type not specified) - ACS with/without revascularisation (follow-up 30 days)												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/777 (0.13%)	3/816 (0.37%)	see comment[5]	2 fewer per 1000 (from 3 fewer to 6 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - STEMI + revascularisation (follow-up 30 days)												

2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/621 (0.16%)	2/659 (0.3%)	see comment[5]	1 fewer per 1000 (from 3 fewer to 13 more)	⊕OOO VERY LOW	IMPORTANT
Stroke (type not specified) - UA/NSTEMI + revascularisation (follow-up 30 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/156 (0%)	1/157 (0.64%)	see comment[5]	5 fewer per 1000 (from 6 fewer to 36 more)	⊕⊕OO LOW	IMPORTANT
Stroke (any type) - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	22/2012 (1.1%)	19/2006 (0.95%)	RR 1.15 (0.63 to 2.13)	2 more per 1000 (from 4 fewer to 11 more)	⊕OOO VERY LOW	IMPORTANT
Need for revascularisation – STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	7/596 (1.2%)	9/634 (1.4%)	RR 0.83 (0.31 to 2.21)	2 fewer per 1000 (from 10 fewer to 17 more)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (definite) - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/596 (0.84%)	3/634 (0.47%)	RR 1.77 (0.43 to 7.39)	4 more per 1000 (from 3 fewer to 30 more)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (type not specified) - STEMI + revascularisation (follow-up 30 days)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	0/50 (0%)	1/50 (2%)	Peto OR 0.14 (0 to 6.82)	17 fewer per 1000 (from 20 fewer to 102 more)	⊕⊕OO LOW	IMPORTANT
Stent thrombosis (definite or probable) - ACS with/without revascularisation (follow-up 1 year)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	26/2012 (1.3%)	20/2006 (1%)	RR 1.30 (0.73 to 2.31)	3 more per 1000 (from 3 fewer to 13 more)	⊕OOO VERY LOW	IMPORTANT
Breathing adverse effects - STEMI + revascularisation (follow-up 30 days)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	5/25 (20%)	0/25 (0%)	Peto OR 8.83 (1.42 to 54.99)	-[3]	⊕⊕OO LOW	IMPORTANT
Bradycardic adverse effects - STEMI + revascularisation (follow-up 30 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	1/25 (4%)	0/25 (0%)	Peto OR 7.39 (0.15 to 372.38)	-[3]	⊕OOO VERY LOW	IMPORTANT
Other adverse effects - STEMI + revascularisation (follow-up 30 days)												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	7/70 (10%)	4/69 (5.8%)	RR 1.59 (0.53 to 4.74)	34 more per 1000 (from 27 fewer to 217 more)	⊕OOO VERY LOW	IMPORTANT

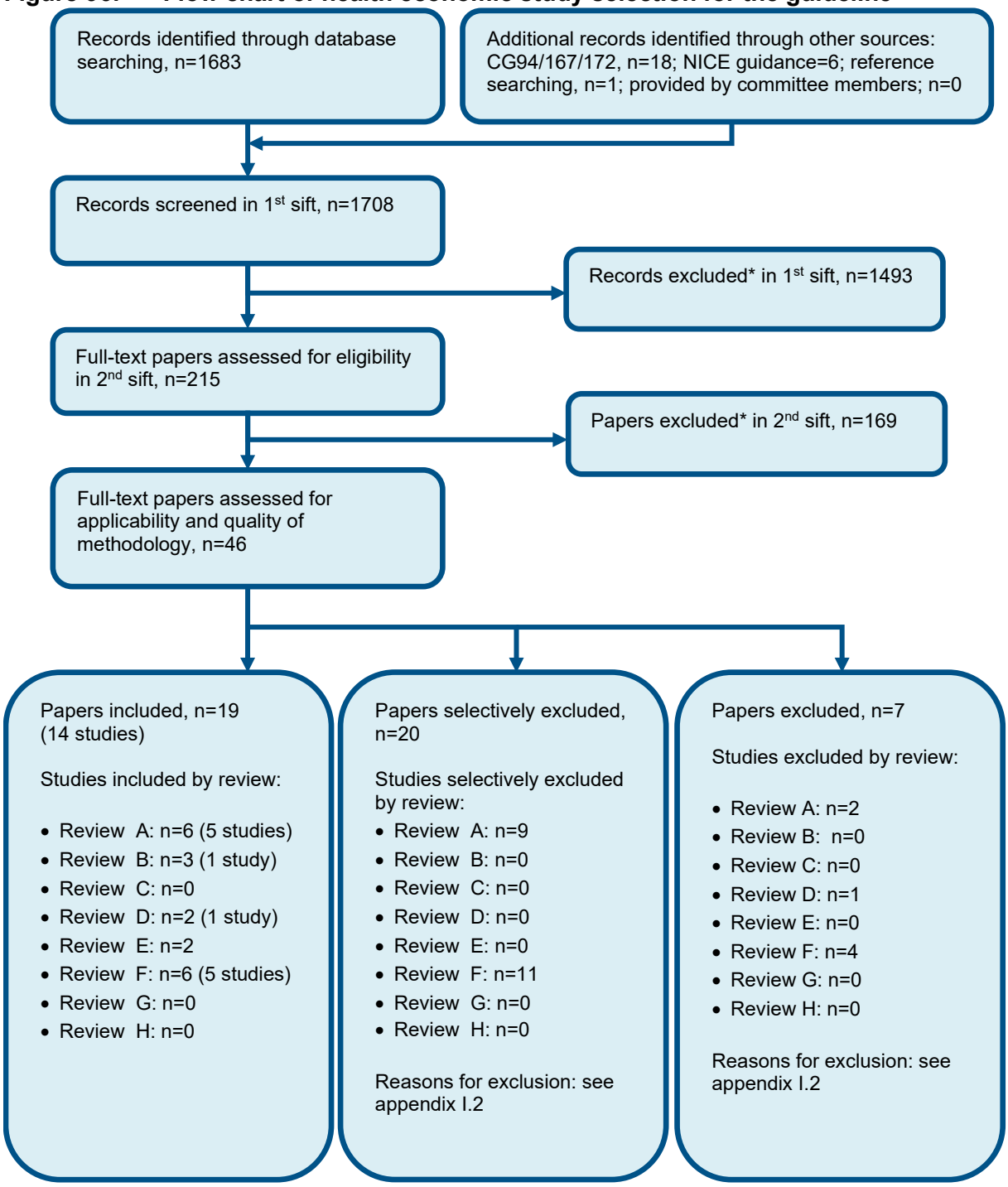
[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Absolute effects could not be calculated due to zero events in one of the arms

[4] Imprecision was assessed by calculating the optimal information size and graded as follows: <80% - very serious imprecision, 80-90%- serious imprecision, >90%- no imprecision

[5] No relative effect due to 0 events. Risk difference calculated in Review Manager

Appendix G: Health economic evidence selection

Figure 96: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Review A = dual-antiplatelet therapy; Review B = early invasive investigation for UA/NSTEMI; Review C = antithrombins in UA/NSTEMI; Review D = bivalirudin in STEMI; Review E = multi-vessel PCI; Review F = drug-eluting stents; Review G = combination of antiplatelets and anticoagulants; Review H = beta-blocker therapy.

Appendix H: Health economic evidence tables

H.1 Ticagrelor + aspirin versus prasugrel + aspirin versus clopidogrel + aspirin

Study	Abdel-Qadir 2015[2]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov cohort state transition model with 1 month cycles. Health states included well post-ACS on DAPT, single antiplatelet therapy at end of 12 months, major bleed, repeat ACS, congestive heart failure and death. It was assumed everyone had a successful PCI procedure. Baseline and treatment effects obtained from data collected in 3 RCTs	**Population:** ACS (STEMI and NSTEMI) patients who have undergone a PCI. **Cohort settings:** Start age: 62 Male: 61% **Intervention 1:** Clopidogrel + aspirin daily for 12 months (dose not reported) **Intervention 2:** Prasugrel + aspirin daily for 12 months (dose not reported) **Intervention 3:** Ticagrelor + aspirin daily for 12 months (dose not reported)	**Total costs (mean per patient):** Intervention 1: £22,325 Intervention 2: £22,787 Intervention 3: £22,915 Incremental (2−1): £462 (95% CI: NR; p=NR) Incremental (3−2): £128 (95% CI: NR; p=NR) **Currency & cost year:** 2012 Canadian dollars (presented here as 2012 UK pounds[(b)]) **Cost components incorporated:** Drug costs, hospitalisation, major bleed, consultations with an emergency physician, a cardiologist and an interventional cardiologist, angiography and	**QALYs (mean per patient):** Intervention 1: 7.41 Intervention 2: 7.43 Intervention 3: 7.50 Incremental (2−1): 0.02 (95% CI: NR; p=NR) Incremental (3−2): 0.07 (95% CI: NR; p=NR)	**ICERs[(c)]** Intervention 3 vs 1: £6,556 per QALY gained (pa) Intervention 2: extendedly dominated Probability most cost-effective option at £11,275/£16,912 threshold: Intervention 1: 17%/8% Intervention 2: 9%/8% Intervention 3: 74%/84% **Analysis of uncertainty:** A wide range of sensitivity analyses around baseline risks, hazard ratios, costs, utilities and all other inputs were undertaken. Ticagrelor remained the most cost-effective option throughout the sensitivity analyses. However, when the hazard ratio for death was greater than 0.89 the ICER associated with ticagrelor compared to clopidogrel exceeded £28,187.

(DISPERSE-2, PLATO and TRITON-TIMI 38). **Perspective:** Canadian health perspective (Ontario Ministry of Health) **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 1 year **Discounting:** Costs: 5%; Outcomes: 5%		percutaneous coronary intervention, transthoracic echocardiogram and follow-up appointments.		
Data sources				
Health outcomes: Baseline event rates were derived from the weighted mean of the event rates in the clopidogrel arm of the TRITON–TIMI 38, DISPERSE-2 and PLATO RCTs. The incidence of events among patients given prasugrel or ticagrelor was modelled by multiplying the baseline rate in the clopidogrel group with the corresponding hazard ratio for each event as determined from each agent's RCT data. Rates of minor bleeding and other minor adverse effects, as well as rates of discontinuation, were determined directly for each agent with the use the TRITON-TIMI 38 and PLATO trial data. Survival beyond 12 months was based on age and sex specific Ontario life tables. **Quality-of-life weights:** Utilities from published literature, tariff unclear and population collected in unclear. Quality of life was independent of intervention used but varied by event experienced. **Cost sources:** Ontario Drug Benefits Formulary, Ontario Case Costing Initiative and Ontario Schedule of Benefits for Physicians.				
Comments				
Source of funding: NR. **Limitations:** 2012 Canadian healthcare perspective may not reflect the current UK context, the cost of clopidogrel used in the model is higher than the cost in the UK, discount rate used not in line with NICE reference case methods and unclear if methods used to derive utilities are consistent with NICE reference case methods. Health states incorporated in the model were different from other models in this area (it does not include stroke as a health state which is a limitation), baseline risks were obtained by calculating the weighted mean of the event rates in the clopidogrel arm of the 3 international trials and the average age used was lower than the UK average. It is unclear where information on resource use was obtained and the analysis does not reflect full body of available evidence for this area as identified in clinical review (based on 3 trials).				
Overall applicability:[(d)] Partially applicable		**Overall quality:**[(e)] Potentially serious limitations		

Abbreviations: ACS = acute coronary syndromes; 95% CI= 95% confidence interval; CUA= cost–utility analysis; DAPT = dual antiplatelet therapy; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT = randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2012 purchasing power parities[175]

(c) When comparing multiple comparators, a fully incremental approach is adopted that compares the treatments sequentially in rank order of effectiveness (or cost).Incremental cost-effectiveness ratios are estimated by dividing the incremental cost by the incremental effect for each consecutively more effective comparator.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Wisloff 2015[303]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA was conducted as part of sensitivity analysis (QALYs); primary analysis used life years **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov cohort state transition model with half year cycles. Health states included PCI, revascularisation, MI, bleeding and death. Efficacy data of prasugrel and ticagrelor compared with clopidogrel was based on the PLATO and TRITON-TIMI-38 RCTs. **Perspective:** Norwegian healthcare perspective **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 1 year	**Population:** ACS patients who have undergone a PCI. **Cohort settings:** Start age: 60 Male: NR **Intervention 1:** Clopidogrel 75mg + aspirin daily for 12 months (300mg clopidogrel loading dose) **Intervention 2:** Prasugrel 10mg + aspirin daily for 12 months (60mg prasugrel loading dose) **Intervention 3:** Ticagrelor 90mg twice daily + aspirin daily for 12 months (180mg ticagrelor loading dose)	**Total costs (mean per patient):** Intervention 1: £12,526 Intervention 2: £14,236 Intervention 3: £16,099 Incremental (2−1): £1,710 (95% CI: NR; p=NR) Incremental (3−2): £1,863 (95% CI: NR; p=NR) **Currency & cost year:** 2014 Norwegian kroner (presented here as 2014 UK pounds[(b)]) **Cost components incorporated:** Drug costs, costs of treatment (MI, revascularisation and bleeding), GP visits and laboratory test costs.	**QALYs (mean per patient):** Intervention 1: 9.54 Intervention 2: 9.82 Intervention 3: 10.12 Incremental (2−1): 0.28 (95% CI: NR; p=NR) Incremental (3−2): 0.30 (95% CI: NR; p=NR) **Life years (mean per patient):** Intervention 1: 11.96 Intervention 2: 12.32 Intervention 3: 12.70 Incremental (2−1): 0.36 (95% CI: NR; p=NR) Incremental (3−2): 0.38 (95% CI: NR; p=NR)	**ICERs[(c)]** Intervention 3 vs 2: £4,903 per life year gained (pa) 95% CI: NR Probability Intervention 3 cost effective (£31,428 threshold): 76% Intervention 2 vs 1: £4,750 per life year gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£31,428 threshold): 27% Intervention 3 vs 2: £6,210 per QALY gained (da) 95% CI: NR Probability Intervention 3 cost effective: NR Intervention 2 vs 1: £6,107 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective: NR **Analysis of uncertainty:** A range of scenario analyses were conducted for the results in relation to cost per LYG and not the cost per QALY results. All analyses showed that

Discounting: Costs: 4%; Outcomes: 4%				ticagrelor remained the most cost-effective option in relation to LYG.
Data sources				
Health outcomes: Does not explain where the estimates of baseline outcomes were derived but it can be assumed it was from the PLATO and TRITON-TIMI 38 trials. The incidence of events among patients given prasugrel or ticagrelor was modelled by applying the HR of ticagrelor and prasugrel from the PLATO and TRITON-TIMI-38 trials to the clopidogrel arm. **Quality-of-life weights:** EQ-5D utility from published data, tariff used not stated and population collected in unclear. Quality of life was independent of intervention used but varied by event experienced. **Cost sources:** Norwegian Medicines Agency and published sources.				
Comments				
Source of funding: Oslo University Hospital. **Limitations:** 2014 Norwegian healthcare perspective may not reflect the current UK context, the cost of clopidogrel used in the model is higher than the cost in the UK, EQ-5D used but unclear if fully in line with NICE reference case methods as tariff not reported and population collected in not stated. Health states incorporated in the model were different from other models in this area (it does not include stroke as a health state which is a limitation), did not give details of how baseline risks were derived, average age used in the model is lower than UK average, it is unclear where resource use was obtained, only conducted sensitivity analyses on results related to life years and not QALYs. Analysis does not reflect full body of available evidence for this area as identified in clinical review (based on 2 trials).				
Overall applicability:[(d)] Partially applicable		**Overall quality:**[(e)] Potentially serious limitations		

Abbreviations: ACS = acute coronary syndromes; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; LYG = life years gained; MI = myocardial infarction; NR= not reported; pa= probabilistic analysis; QALYs= quality-adjusted life years; RCT = randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Converted using 2014 purchasing power parities[175]

(c) When comparing multiple comparators, a fully incremental approach is adopted that compares the treatments sequentially in rank order of effectiveness (or cost).Incremental cost-effectiveness ratios are estimated by dividing the incremental cost by the incremental effect for each consecutively more effective comparator.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

H.2 Ticagrelor + aspirin versus clopidogrel + aspirin

Study	**NICE TA236 2011[125(a)]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A one-year decision tree based on the data from the PLATO trial, with the following events: death from any cause, non-fatal stroke, non-fatal MI and no further event. This was followed by a Markov model for long term extrapolation, which included the following health states; no event, non-fatal MI, post MI, non-fatal stroke, post-stroke and dead. Non-fatal MI and non-fatal stroke were tunnel states to allow for worse prognosis in the first year. Bleeding was captured through decrements in utilities and additional costs applied within each health state. Treatment effects and resource use were based on data collected within PLATO RCT; adjustments were made to reflect UK practice where necessary. **Perspective:** UK NHS	**Population:** ACS patients (STEMI, NSTEMI and UA), including those managed medically or those with PCI or CABG **Cohort settings:** Start age: 70 Male: 64.6% **Intervention 1:** Clopidogrel 75mg + aspirin daily for 12 months (300-600mg clopidogrel loading dose) **Intervention 2:** Ticagrelor 90mg twice daily + aspirin for 12 months (180mg ticagrelor loading dose)	**Total costs (mean per patient):** *All ACS:* Intervention 1: £13,737 Intervention 2: £14,135 Incremental (2−1): £398 (95% CI: NR; p=NR) *STEMI subgroup:* Intervention 1: £15,483 Intervention 2: £15,822 Incremental (2−1): £339 (95% CI: NR; p=NR) *NSTEMI subgroup:* Intervention 1: £13,140 Intervention 2: £13,653 Incremental (2−1): £513 (95% CI: NR; p=NR) *UA subgroup*: Intervention 1: £12,419 Intervention 2: £12,907 Incremental (2−1): £488 (95% CI: NR; p=NR) **Currency & cost year:** 2008/09 UK pounds	**QALYs (mean per patient):** *All ACS:* Intervention 1: 6.275 Intervention 2: 6.382 Incremental (2−1): 0.107 (95% CI: NR; p=NR) *STEMI subgroup:* Intervention 1: 7.567 Intervention 2: 7.687 Incremental (2−1): 0.120 (95% CI: NR; p=NR) *NSTEMI subgroup:* Intervention 1: 5.345 Intervention 2: 5.443 Incremental (2−1): 0.098 (95% CI: NR; p=NR) *UA subgroup:* Intervention 1: 7.079 Intervention 2: 7.170 Incremental (2−1): 0.091 (95% CI: NR; p=NR)	*All ACS ICER:* £3,805 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/£30K threshold): 99.9%/NR *STEMI subgroup ICER:* £5,230 per QALY gained (da) 95% CI: NR Probability intervention 2 cost effective (£20K/£30K threshold): NR/NR *NSTEMI subgroup ICER:* £2,825 per QALY gained (da) 95% CI: NR Probability intervention 2 cost effective (£20K/£30K threshold): NR/NR *UA subgroup ICER:* £5,374 per QALY gained (da) 95% CI: NR Probability intervention 2 cost effective (£20K/£30K threshold): NR/NR **Analysis of uncertainty:** A wide range of sensitivity analyses around event rates, hazard ratios, utilities and costs were undertaken. This showed that varying the parameters did not impact the conclusions apart from the cost of the 'no further event' health state. Setting the cost of this state in the ticagrelor + aspirin arm to its lowest resulted in ticagrelor + aspirin being dominant. When it was set to its

Time horizon: Lifetime **Treatment effect duration:**[(b)] 1 year. The model assumed that the beneficial effect of ticagrelor does not continue beyond one year. **Discounting:** Costs: 3.5%; Outcomes: 3.5%		**Cost components incorporated:** Drug costs (ticagrelor, clopidogrel and aspirin), hospitalisation, investigations, blood product and reoperations due to bleeding and drugs, event costs (stroke and MI).		lowest for the clopidogrel + aspirin arm the ICER was £21,000 per QALY gained. Different scenario analyses were conducted such as varying the discount rates and using published utility values rather than those derived from the PLATO trial, but they did not affect the results significantly. **ICERs using alternative time horizons:**

	20 yrs	10 yrs	5 yrs	1 yr
All ACS	£3,705	£4,182	£6,075	£36,177
STEMI	£2,847	£3,334	£4,946	£31,933
NSTEMI	£5,233	£5,727	£8,162	£45,810
UA	£5,410	£6,484	£10,172	£78,288

Data sources

Health outcomes: Baseline event rates for the clopidogrel + aspirin arm and treatment effects with ticagrelor + aspirin were derived from the PLATO RCT. For the 1-year decision tree a parametric time-to-event survival model with a Weibull distribution was used to determine the baseline risk. The HRs from the PLATO RCT were then applied to determine effectiveness of ticagrelor. In the Markov model, transition probabilities were estimated from the Myocardial Ischaemia National Audit Project and the General Practice Research database and UK standard life tables. The average age of patients in the PLATO trial was lower than the average age of patients with ACS in the UK; therefore age was adjusted to reflect the UK in the decision tree. **Quality-of-life weights:** EQ-5D was administered to participants in the PLATO health economics and quality of life sub-study, using the UK tariff, quality of life was independent of intervention used but varied by event experienced. **Cost sources:** UK National sources and published studies.

Comments

Source of funding: AstraZeneca UK Ltd. **Limitations:** International resource use from 2006-2008 and 2008/09 UK unit costs may not reflect current UK practice. UK practice is to give a clopidogrel loading dose of 600mg and the study allowed a clopidogrel loading dose of 300-600mg with only one fifth of patients received 600mg. Mean age of patients in the PLATO trial was lower than UK average and proportion of older patients different to UK setting but an age-adjusted event rate was used in the clopidogrel arm to attempt to address this. Analysis does not reflect full body of available evidence for this area as identified in clinical review; main analysis based on a single study (PLATO). Uncertainty in estimates of effectiveness due to participants being

able to leave the trial early and not followed up for 12 months - which effects the long-term patient outcomes in the Markov model. The health economic sub-study was used to derive data on resource use and utilities; however there was no information on how this sub-study was recruited for. Study funded by AstraZeneca.

Overall applicability:(c) Partially applicable **Overall quality:**(d) Potentially serious limitations

Abbreviations: ACS = Acute coronary syndromes; CABG = coronary artery bypass graft; CI = confidence interval; CUA = cost–utility analysis; da = deterministic analysis; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST-elevation myocardial infarction; pa = probabilistic analysis; PCI = percutaneous coronary intervention; QALY = quality-adjusted life years; RCT = randomised controlled trial; STEMI = ST-elevation myocardial infarction; UA = unstable angina

(a) Manufacturer submission for NICE TA236

(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Janzon 2011[64]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** A one-year decision tree based on the data from the PLATO trial, with the following events: death from any cause, non-fatal stroke, non-fatal MI and no further event. This was followed by a Markov model for long term extrapolation, which included the following health states; no event, non-fatal MI, post MI, non-	**Population:** ACS patients intended for non-invasive therapy(b) **Cohort settings:** Start age: 62 Male: 71.6% **Intervention 1:** Clopidogrel 75mg + aspirin daily for 12 months (300-600mg clopidogrel loading dose) **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £12,972 Intervention 2: £13,440 Incremental (2−1): £468 (95% CI: NR; p=NR) **Currency & cost year:** 2010/11 UK pounds **Cost components incorporated:** Drug costs (ticagrelor, clopidogrel and aspirin), bed days due to hospitalisation,	**QALYs (mean per patient):** Intervention 1: 8.44 Intervention 2: 8.60 Incremental (2−1): 0.16	£2,925 per QALY gained (da) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): 99.9%/99.9% **Analysis of uncertainty:** Alternative scenarios were explored by altering the value of input parameters not associated with sampling uncertainty (therefore not varied in the probabilistic sensitivity analysis). These scenarios did not change conclusions about cost effectiveness. Using the treatment effect observed in the non-invasive patients rather than the overall treatment effect for all ACS patients did not change results and resulted in an ICER of £2,694 per QALY gained.

fatal stroke, post-stroke and dead. Treatment effects and resource use were based on data collected within the PLATO RCT. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 1 year. The model assumed that the beneficial effect of ticagrelor does not continue beyond one year. **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Ticagrelor 90mg twice daily + aspirin for 12 months (180mg ticagrelor loading dose)	investigations, blood product and reoperations due to bleeding and event costs (stroke and MI).		
Data sources				
Health outcomes: Baseline event rates for the clopidogrel + aspirin arm and treatment effects with ticagrelor + aspirin were derived from the PLATO RCT. For the 1-year decision tree survival analysis was used to determine the baseline risk. The HRs from the PLATO RCT were then applied to determine effectiveness of ticagrelor. In the Markov model, transition probabilities were estimated by extrapolating out the observed hazard function of clopidogrel-treated patients in PLATO beyond 1 year of follow-up and using UK standard life tables. **Quality-of-life weights:** EQ-5D was administered to participants in the PLATO health economics and quality of life sub-study, using the UK tariff, quality of life was independent of intervention used but varied by event experienced. **Cost sources:** UK National sources and published studies.				
Comments				
Source of funding: AstraZeneca UK Ltd. **Limitations:** International resource use from 2006-2008 and 2010 UK unit costs may not reflect current UK practice. Only looks at patients intended for non- invasive management. Start age used in the cohort is younger than the average age of UK ACS patients and does not include prasugrel in the analysis. Does not state if bleeding was incorporated in the model, analysis does not reflect full body of available evidence for this area as identified in clinical review; analysis based on a single study (PLATO). Study was funded by AstraZeneca.				
Overall applicability:[(c)] Partially applicable		**Overall quality:**[(d)] Potentially serious limitations		

Abbreviations: ACS = Acute coronary syndromes; CI = confidence interval; CUA = cost–utility analysis; da = deterministic analysis; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; QALY = quality-adjusted life years; RCT = randomised controlled trial

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Although patients were intended for non-invasive management approximately half of the patients had coronary angiography, a third had PCI, and one tenth had CABG during the course of the study.
(c) Directly applicable / Partially applicable / Not applicable
(d) Minor limitations / Potentially serious limitations / Very serious limitations

H.3 Ticagrelor + aspirin versus prasugrel + aspirin

Study	NICE TA236 2011[125(a)]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Based on the results of a published indirect comparison of the TRITON-TIMI-38 and PLATO trials[18], and only analysed patients who were invasively managed. The model had the same health states as stated in the original analysis (see above). **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(b)] 1 year **Discounting:** Costs: 3.5%; Outcomes: 3.5%	**Population:** ACS patients managed invasively (angiography followed by PCI/CABG if indicated) **Cohort settings:** Start age: 70 Male: 64.6% **Intervention 1:** Prasugrel 65mg + aspirin daily for 12 months (60mg prasugrel loading dose) **Intervention 2:** Ticagrelor 90mg twice daily + aspirin for 12 months (180mg ticagrelor loading dose)	**Total costs (mean per patient):** Intervention 1: £7,845 Intervention 2: £8,072 Incremental (2−1): £277 (95% CI: NR; p=NR) **Currency & cost year:** 2008/09 UK pounds **Cost components incorporated:** Drug costs (ticagrelor, prasugrel and aspirin), hospitalisation, investigations, blood product and reoperations due to bleeding and drugs, event costs (stroke and MI).	**QALYs (mean per patient):** Intervention 1: 8.045 Intervention 2: 8.110 Incremental (2-3): 0.065 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £3,482 per QALY gained (da) 95% CI: NR Probability ticagrelor cost effective (£20K/30K threshold): 91.6%/NR **Analysis of uncertainty:** Deterministic results using a different time horizon showed that ticagrelor remained cost-effective at 20, 10 and 5 years as demonstrated in the table below: **20 yrs** | **10 yrs** | **5 yrs** £3,598 | £4,562 | £7,047

Data sources
Health outcomes: Baseline event rates were taken from the PLATO RCT. Relative risks were converted from the odds ratios for death, MI and stroke taken from the published indirect comparison and applied to the baseline event rates to give the event rate for prasugrel. **Quality-of-life weights:** Utilities from published literature; tariff unclear; collected in relevant population. Quality of life was independent of intervention used but varied by event experienced. **Cost sources:** UK National sources and published studies.
Comments
Source of funding: AstraZeneca UK Ltd. **Limitations:** International resource use from PLATO RCT which recruited 2006-2008 and 2008/09 UK unit costs may not reflect current UK practice. Does not include clopidogrel in the analysis. Baseline event rates were taken from the PLATO international trial, which may not reflect UK practice, however the analysis used an age-adjusted event rate to address this. Relative treatment effects for prasugrel compared to ticagrelor were estimated from an indirect comparison using studies that compared each drug to clopidogrel; while using an indirect comparison is not necessarily inappropriate the manufacturer highlighted issues with the indirect comparison and the technology appraisal committee did not think the analysis was appropriate due to differences in the target populations of the two trials, differences in the usage of clopidogrel (dosing and timing) and differences in the assessment of MI. Health state costs were calculated based on resource use collected in ticagrelor arm of the PLATO trial; in the absence of a head-to-trial collecting such data, it was assumed that these costs would be the same with prasugrel. Study was funded by AstraZeneca.
Overall applicability:[(c)] Partially applicable **Overall quality:**[(d)] Potentially serious limitations

Abbreviations: CABG = coronary artery bypass graft; CCA= cost–consequences analysis; CEA= cost-effectiveness analysis; 95% CI= 95% confidence interval; CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER= incremental cost-effectiveness ratio; MI = myocardial infarction; NR= not reported; PCI = percutaneous coronary intervention; QALYs= quality-adjusted life years

(a) Manufacturer submission for NICE TA236. Note: this was not the primary analysis in the TA.

(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

H.4 Prasugrel + aspirin versus clopidogrel + aspirin

Study	Greenhalgh 2015[54(a)]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model structure with two phases; the first phase models the within trial period and health states included bleeding, non-fatal stroke, non-fatal MI and cardiovascular/bleed death. Treatment effects based on the TRITON-TIMI 38 RCT for the initial 12 month analysis. For extrapolation beyond this point data from the CAPRIE trial was used and health states included non-fatal MI, non-fatal stroke, no prior events, prior stroke, prior MI and death. Adjustments were made to reflect UK practice where necessary **Perspective:** UK NHS **Time horizon:** lifetime	**Population:** Patients with ACS undergoing primary or delayed PCI **Cohort settings:** *STEMI patients with diabetes:* Start age: 58.0 (male); 60.9 (female) Male: 75.4% *STEMI patients without diabetes:* Start age: 55.5 (male); 59.1 (female) Male: 84.0% *UA/NSTEMI patients with diabetes:* Start age: 59.3 (male); 61.5 (female) Male: 68.7% *UA/NSTEMI patients without diabetes:* Start age: 57.1 (male); 60.1 (female) Male: 80.3% **Intervention 1:** Clopidogrel 75mg daily + aspirin for 12 months	**Total costs (mean per patient):** *STEMI patients with diabetes:* Intervention 1: £19,904 Intervention 2: £20,351 Incremental (2−1): £447 (95% CI: NR; p=NR) *STEMI patients without diabetes:* Intervention 1: £21,167 Intervention 2: £21,722 Incremental (2−1): £555 (95% CI: NR; p=NR) *UA/NSTEMI patients with diabetes:* Intervention 1: £19,015 Intervention 2: £18,939 Incremental (2−1): –£77 (95% CI: NR; p=NR) *UA/NSTEMI patients without diabetes:* Intervention 1: £20,328 Intervention 2: £20,576 Incremental (2−1): £248 (95% CI: NR; p=NR) **Currency & cost year:** 2012/13 UK pounds	**QALYs (mean per patient):** *STEMI patients with diabetes:* Intervention 1: 10.05 Intervention 2: 10.33 Incremental (2−1): 0.28 (95% CI: NR; p=NR) *STEMI patients without diabetes:* Intervention 1: 10.95 Intervention 2: 11.03 Incremental (2−1): 0.08 (95% CI: NR; p=NR) *UA/NSTEMI patients with diabetes:* Intervention 1: 9.92 Intervention 2: 10.10 Incremental (2−1): 0.18 (95% CI: NR; p=NR) *UA/NSTEMI patients without diabetes:* Intervention 1: 10.66 Intervention 2: 10.71 Incremental (2−1): 0.05 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** *STEMI patients with diabetes:* £1,732 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR *STEMI patients without diabetes:* £7,073 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR *UA/NSTEMI patients with diabetes:* Intervention 2 dominant 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR *UA/NSTEMI patients without diabetes:* £4,154 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost effective (£20K/30K threshold): NR/NR **Analysis of uncertainty:** Univariate sensitivity analyses were performed on all model variables subject to uncertainty, and prasugrel remained cost-effective. **ICERs using alternative time horizons:**

Treatment effect duration:[b] 1 year **Discounting:** Costs: 3.5%; Outcomes: 3.5%	(300mg clopidogrel loading dose) **Intervention 2:** Prasugrel 10mg daily + aspirin for 12 months (60mg prasugrel loading dose)	**Cost components incorporated:** Drug costs, repeat hospitalisations, health care costs associated with each health state.		

20 yrs	10 yrs	5 yrs	1 yr
STEMI with diabetes			
£1,537	£2,139	£4,603	£31,915
STEMI without diabetes			
£7,670	£13,370	£29,607	£224,302
UA/NSTEMI with diabetes			
Dominant	Dominant	£2,846	£76,856
UA/NSTEMI without diabetes			
£5,688	£14,276	£52,288	£1,101,662

Data sources

Health outcomes: Based on treatment follow-up in TRITON-TIMI 38 RCT, risk equations were developed in order to estimate the risk of primary efficacy and safety events for the cohorts of patients receiving prasugrel and clopidogrel. Separate risk equations for the primary end point events were modelled for UA/NSTEMI and STEMI populations. These analyses used logistic models for events occurring within 3 days, and Weibull models over the remainder of the trial period (up to 12 months). For extrapolating long-term vascular events, data from the CAPRIE trial was used (this was used for TA210 - Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events). In TA210, the MI sub-population model was based on CAPRIE data and used at an individual patient simulation approach. However, for this analysis the model used in TA210 was adapted to employ a long-term Markov model. Differences in age between the TRITON-TIMI 38 trial and UK population were accounted for by adjusting the initial health state utilities for each subgroup. **Quality-of-life weights:** EQ-5D, UK population valuation tariff, quality of life was independent of intervention used but varied by event experienced. EQ-5D data was obtained from the PLATO trial (ticagrelor vs clopidogrel) as the sub-study in the TRITON-TIMI 38 RCT did not recruit enough participants. **Cost sources:** NHS reference costs, NHS drug tariff and MIMS.

Comments

Source of funding: NIHR. **Limitations:** International resource use from 2004-2007 and 2012 UK unit costs may not reflect current UK practice. The trial used a clopidogrel loading dose of 300mg instead of 600mg which does not reflect UK practice and analysis does not include ticagrelor. Mean age of patients in the TRITON-TIMI 38 trial was different to UK average but this was accounted for by adjusting the initial health state utilities of each subgroup. Did not use new cost data for the relevant year; instead unit costs from the previous TA report were inflated to 2012 prices. Analysis does not reflect full body of available evidence identified in clinical review; analysis based on a single study (TRITON-TIMI 38).

Overall applicability:[c] Partially applicable **Overall quality:**[d] Potentially serious limitations

Abbreviations: ACS = Acute coronary syndromes; 95% CI = confidence interval; CUA = cost–utility analysis; EQ-5D = Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; NR = not reported; NSTEMI = non-ST-elevation myocardial

infarction; pa = probabilistic analysis; PCI = percutaneous coronary intervention; QALY = quality-adjusted life years; RCT = randomised controlled trial; STEMI = ST-elevation myocardial infarction; UA = unstable angina

(a) ERG analysis for NICE TA317

(b) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 29: Studies excluded from the clinical review

Study	Exclusion reason
Abaci 2015[1]	Not available
Abergel 2010[3]	Narrative review; references checked
Agewall 2011[4]	Narrative review; references checked
Alexopoulos 2012[5]	Incorrect study population (patients with ACS and high on-treatment platelet reactivity while on clopidogrel after PCI)
Alexopoulos 2013[9]	Incorrect study population (people with ACS and high on-treatment platelet reactivity while on clopidogrel and undergoing PCI)
Alexopoulos 2015[7]	Study population with HPR while on treatment (mostly with clopidogrel)
Alexopoulos 2016[6]	Incorrect study comparison and no relevant outcomes
Amico 2016[10]	Secondary evaluation of PLATO
Andell 2015[11]	PLATO post-hoc subgroup analysis of patients with COPD
Antman 2008[13]	TRITON analysis with no additional relevant outcomes
Bavishi 2015[14]	Meta-analysis; references checked
Becker 2011[15]	No additionally relevant outcomes from PLATO
Bellavia 2017[16]	PLATO secondary analysis with no additional relevant outcomes
Bhatt 2009[17]	Narrative review; references checked
Biondi-Zoccai 2011[18]	Indirect comparison meta-analysis; references checked
Bonaca 2016[19]	Incorrect study comparison
Brener 2014[21]	Incorrect study comparison
Briasoulis 2016[22]	Systematic review; references checked
Bundhun 2017[24]	Systematic review; references checked
Bundhun 2018[23]	Meta-analysis; references checked
Cannon 2010[25]	PLATO ACS substudy with no additional relevant outcomes
Cayla 2017[27]	Incorrect study comparison
Chen 2015[28]	Letter publication only
Chin 2010[31]	TRILOGY study design and rationale only
Chin 2013[29]	No usable data from PLATO cost effectiveness analysis
Chin 2016[30]	TRILOGY subgroup analysis of people with stroke
Choi 2017[32]	Incorrect study comparison
Costa 2015[34]	Incorrect study comparison
Dalby 2017[35]	TRILOGY subgroup analysis in people with diabetes
Deharo 2013[43]	Letter publication only
Diodati 2014[45]	Incorrect study comparison
Fanari 2015[46]	Narrative review; references checked
Ferri 2016[47]	Study design and rationale only
Fluschnik 2018[48]	Narrative review; references checked
Fonarow 2016[49]	Cancelled by reviewer

Study	Exclusion reason
Gan 2015[50]	Meta-analysis; references checked
Gasche 2013[51]	No usable data from PLATO cost effectiveness analysis
Ge 2010[52]	Study design and rationale only
Husted 2012[58]	PLATO substudy in older adults
James 2009[59]	Study design and rationale only
James 2010[60]	PLATO substudy in patients with diabetes
James 2010[61]	PLATO substudy in patients with chronic kidney disease
James 2011[62]	PLATO ACS substudy with no additional relevant outcomes
James 2012[63]	PLATO substudy in patients with a history of stroke or TIA
Jing 2018[66]	Meta-analysis; reference checked
Kang 2015[68]	PLATO subgroup analysis for Asian and non-Asian patients
Ketchum 2011[70]	Systematic review; references checked
Khan 2016[71]	Systematic review; references checked
Khasa 2016[72]	Incorrect study population and treatment switching
Kim 2017[74]	No relevant outcomes
Kim 2018[73]	No relevant outcomes
Kimura 2015[75]	Incorrect study population (excluded ACS)
Kohli 2013[78]	PLATO analysis with no additional relevant outcomes (recurrent cardiovascular events not prespecified in review protocol)
Kohli 2014[77]	TRITON analysis of discharge aspirin dose
Kotsia 2014[79]	PLATO analysis by extent of coronary artery disease
Kozinski 2014[80]	Incorrect study design
Kubo 2016[81]	Incorrect study design
Kulik 2009[82]	Systematic review; incorrect study comparison
Kunadian 2013[83]	PLATO substudy of angiographic outcomes
Laine 2015[85]	No relevant outcomes
Lau 2017[86]	Meta-analysis; references checked
Lee 2013[89]	Protocol only
Lee 2014[87]	Incorrect study comparison
Lee 2014[88]	Incorrect study population and comparison
Lee 2017[92]	Incorrect study comparison
Lee 2017[90]	Incorrect study comparison; design and rationale only
Lee 2018[91]	Meta-analysis; references checked
Lemesle 2015[94]	Systematic review; references checked
Leonardi 2012[95]	Incorrect comparison; study design and rationale only
Levin 2013[96]	PLATO substudy - no usable outcomes
Li 2015[98]	No relevant outcomes before switching treatments
Li 2015[97]	Not available
Li 2016[101]	Incorrect study comparison; protocol only
Li 2018[99]	No relevant outcomes
Lopes 2016[104]	TRILOGY substudy of spontaneous myocardial infarction
Mahaffey 2014[105]	No additional relevant outcomes for PLATO
Mahoney 2010[106]	No useable additional relevant outcomes for TRITON. No usable additional relevant TRITON outcomes
Mannacio 2012[107]	Incorrect study population and comparison
Mariani 2009[108]	No additional relevant outcomes to TRITON

Study	Exclusion reason
Mega 2010[109]	TRITON pharmacogenetic analysis
Melloni 2016[110]	TRILOGY substudy of patients with chronic kidney disease
Misumida 2018[111]	Meta-analysis; references checked
Modi 2012[112]	Not available
Mohammad 2010[113]	Narrative review; references checked
Montalescot 2010[115]	Incorrect study comparison
Mont'alverne-Filho 2016[114]	No relevant outcomes
Morrow 2009[117]	TRITON analysis with no additional relevant outcomes
Motovska 2018[118]	Incorrect study design related to switching treatments
Murphy 2008[120]	TRITON secondary analysis of recurrent endpoints, no additional prespecified outcomes
Musallam 2016[121]	Incorrect study population
Nakamura 2015[122]	PRASFIT substudy with no additional relevant outcomes
NCT 2008[136]	Not available
NCT 2009[151]	Not available
NCT 2009[135]	Not available
NCT 2011[145]	Not available
NCT 2011[159]	Not available
NCT 2012[146]	Not available
NCT 2013[155]	Not available
NCT 2013[142]	Not available
NCT 2013[138]	Not available
NCT 2013[160]	Not available
NCT 2013[157]	Not available
NCT 2013[162]	Not available
NCT 2013[128]	Not available
NCT 2014[144]	Not available
NCT 2014[158]	Not available
NCT 2014[140]	Not available
NCT 2014[134]	Not available
NCT 2014[154]	Not available
NCT 2014[127]	Not available
NCT 2014[139]	Not available
NCT 2014[156]	Not available
NCT 2014[161]	Not available
NCT 2014[132]	Not available
NCT 2014[126]	Not available
NCT 2015[133]	Not available
NCT 2015[150]	Not available
NCT 2015[137]	Not available
NCT 2015[163]	Not available
NCT 2015[153]	Not available
NCT 2015[141]	Not available
NCT 2015[152]	Not available
NCT 2016[129]	Not available
NCT 2016[149]	Not available

Study	Exclusion reason
NCT 2016[148]	Not available
NCT 2017[131]	Not available
NCT 2017[164]	Not available
NCT 2017[143]	Not available
NCT 2017[130]	Not available
NCT 2018[147]	Not available
Neumann 2009[165]	Systematic review; references checked
Nicolau 2015[167]	TRILOGY substudy of proton pump inhibitor use
Nikolic 2013[168]	No usable data from PLATO cost effectiveness analysis
Nishikawa 2015[169]	PRASFIT post-hoc analysis with no additional relevant outcomes
O'Donoghue 2016[170]	Incorrect study comparison
Ogawa 2016[171]	PRASFIT post-hoc analysis with no additional relevant outcomes
Ojeifo 2013[172]	TRITON study of statins and calcium channel blocker use
Orban 2016[174]	Incorrect study design
Palacio 2012[176]	Systematic review; incorrect study comparison
Pandit 2014[177]	Systematic review; incorrect study comparison
Paré 2012[178]	Incorrect study comparison
Park 2010[182]	Incorrect study comparison
Park 2014[180]	Protocol only; no relevant outcomes prespecified
Park 2016[181]	No relevant outcomes
Park 2018[179]	Study design and rationale only
Parker 2017[183]	Incorrect study comparison
Patel 2009[186]	Systematic review; references checked
Patel 2015[187]	PLATO substudy of patients with peripheral artery disease
Patti 2013[188]	Incorrect study comparison
Pickard 2008[190]	Narrative review; incorrect study comparison
Pollack 2017[191]	PLATO subgroup analysis on time to drug administration in relation to angiography not relevant to review question
Pourdjabbar 2017[192]	Incorrect study comparison
Pouwels 2018[193]	Evaulation only
Pride 2009[194]	TRITON substudy of patients undergoing PCI without stent implantation
Qaderdan 2015[195]	Study design and rationale only
Rafiq 2012[196]	Incorrect study comparison; protocol only
Rafique 2016[197]	Network meta-analysis; references checked
Refiker 2011[198]	Incorrect study comparison; commentary only
Ren 2012[199]	Not available
Ren 2016[200]	Incorrect study design
Reynard 2017[201]	Abstract only for systematic review
Rodriguez 2018[202]	Narrative review; references checked
Roe 2013[205]	TRILOGY substudy of older adults
Roe 2016[204]	TRILOGY substudy of neoplasm events
Roffman 2016[206]	Narrative review; references checked
Rognoni 2016[207]	Narrative review; references checked
Rossington 2016[208]	Systematic reivew; references checked
Rudolph 2017[209]	No relevant outcomes

Study	Exclusion reason
Ruff 2012[210]	TRITON substudy by different world regions
Saint Etienne 2013[211]	Incorrect study comparison
Saito 2014[212]	Low dosage prasugrel
Sakurai 2017[213]	Meta-analysis; references checked
Salisbury 2013[214]	TRITON risk modelling substudy
Sardar 2014[215]	Meta-analysis; references checked
Sardella 2015[216]	Incorrect study population (excluded ACS)
Sardella 2017[217]	No relevant outcomes
Sarkees 2009[218]	Systematic reviewl references checked
Sarkees 2010[219]	Systematic review; references checked
Saucedo 2013[220]	No relevant outcomes
Saw 2016[222]	Incorrect study comparison and population
Sawlani 2017[223]	Incorrect study comparison and population
Schnorbus 2014[224]	Protocol only; no relevant outcomes prespecified
Scirica 2011[227]	PLATO ECG substudy
Scirica 2018[226]	PLATO substudy of ECG abnormalities
Serebruany 2012[228]	Narrative review; references checked
Serebruany 2013[230]	Incorrect study comparison; secondary evaluation only
Serebruany 2015[229]	Meta-analysis; references checked
Serebruany 2016[231]	Narrative review; references checked
Servi 2015[40]	Letter only
Servi 2016[41]	TRITON substudy of culprit lesion site
Shah 2017[232]	Network meta-analysis; references checked
Shahzeb 2015[233]	Incorrect study population
Siller-Matula 2011[234]	Systematic review; references checked
Siller-Matula 2017[235]	Systematic review; references checked
Singh 2016[236]	Network meta-analysis; references checked
Smith 2012[237]	TRITON substudy with no additional relevant outcomes
Solomon 2010[238]	Commentary only; no usable outcome data
Song 2017[239]	Incorrect study design
Sorich 2010[240]	TRITON substudy by genotype
Spartalis 2017[241]	Systematic review; references checked
Spinar 2015[242]	Not available
Spinar 2015[243]	Not available
Steblovnik 2016[244]	Incorrect study population
Steg 2013[246]	PLATO substudy with no additional relevant outcomes
Steg 2013[245]	Incorrect study comparison
Steiner 2012[248]	Network meta-analysis; references checked
Storey 2010[250]	PLATO substudy with no additional relevant outcomes
Storey 2011[252]	PLATO substudy with no additional relevant outcomes
Storey 2011[251]	PLATO substudy with no additional relevant outcomes
Storey 2014[253]	PLATO substudy with no additional relevant outcomes
Storey 2016[249]	Incorrect study comparison
Sudlow 2009[254]	Cochrane systematic review, incorrect study comparison and population
Sun 2008[258]	Systematic review; incorrect study comparison

Study	Exclusion reason
Sun 2010[256]	Incorrect study comparison
Sun 2011[257]	Incorrect study comparison; letter only
Sun 2017[255]	Systematic review; references checked
Sweeny 2017[259]	No relevant outcomes
Tan 2014[261]	Not available
Tan 2017[260]	Systematic review; references checked
Tang 2014[264]	Meta-analysis; references checked
Tang 2015[265]	Systematic review; incorrect study comparison
Tang 2016[262]	Meta-analysis; references checked
Tarantini 2018[266]	Systematic review; references checked
Theidel 2013[267]	No usable data from PLATO cost effectiveness analysis
Torngren 2013[268]	Incorrect study design
Udell 2014[269]	TRITON substudy of outcomes by primary versus secondary PCI
Vaduganathan 2017[271]	Incorrect study comparison
Vaduganathan 2017[270]	Incorrect study comparison
Valenti 2015[272]	Incorrect study design
Varenhorst 2012[274]	PLATO substudy with no additional relevant outcomes
Varenhorst 2014[273]	PLATO substudy with no additional relevant outcomes
Velders 2016[275]	PLATO post-hoc subgroup analysis of patients with STEMI who underwent PPCI
Verdoia 2014[277]	Meta-analysis; incorrect study comparison
Verdoia 2016[276]	Meta-analysis; references checked
Verma 2015[278]	Meta-analysis; incorrect study comparison
Vito 2016[279]	Incorrect study comparison
Vlaar 2008[280]	Systematic review; references checked
Voeltz 2013[281]	Incorrect study comparison
Vogel 2017[282]	Narrative review; incorrect study comparison
Waha 2016[283]	Incorrect study comparison; study design and rationale only
Wallentin 2010[285]	PLATO genetic substudy
Wallentin 2014[286]	PLATO substudy with no additional relevant outcomes
Walter 2008[287]	Incorrect study population and comparison, and no relevant outcomes
Wang 2018[288]	No relevant outcomes
Washam 2014[292]	Systematic review; incorrect study comparison
Watti 2017[293]	Meta-analysis; references checked
Weber 2011[294]	Incorrect study comparison
Wein 2017[295]	Incorrect study comparison
Welsh 2012[296]	Incorrect study comparison
Westman 2017[297]	Network meta-analysis; references checked
White 2012[299]	Incorrect study comparison
White 2015[298]	Incorrect study comparison
White 2016[300]	TRILOGY subanalysis by frailty
Wilcox 2014[301]	TRITON subanalysis of 10mg indicated cohort
Winter 2014[302]	No relevant outcomes
Wisloff 2011[304]	Systematic review; references checked
Wiviott 2005[305]	Patient population not defined for inclusion of ACS

Study	Exclusion reason
Wiviott 2007[310]	Study population with angina but no breakdown of results for unstable angina
Wiviott 2008[307]	TRITON subanalysis of patients with bare metal and drug eluting stents
Wiviott 2008[306]	TRITON subanalysis of patients with/without diabetes
Wiviott 2011[309]	TRITON survival analysis by core cohort, noncore and contraindicated
Wiviott 2013[311]	PLATO subgroup analysis with/without angiography not relevant to review question
Wu 2017[314]	Patients with coronary heart disease and high on-treatment platelet reactivity while on clopidogrel, following elective PCI
Wu 2018[312]	Meta-analysis; references checked
Xanthopoulou 2016[315]	Narrative review; references checked
Xia 2015[316]	Not available
Xiong 2015[317]	Incorrect intervention (very high maintanence dose of clopidogrel)
Yan 2018[318]	TRILOGY post-hoc subanalysis of outcomes with early drug discontinuation
Yang 2017[320]	Meta-analysis; references checked
Yang 2017[319]	No relevant outcomes
Ye 2014[322]	Network meta-analysis; references checked
Yuan 2016[323]	Not available
Yun 2017[324]	No relevant outcomes
Zaccardi 2015[325]	Meta-analysis; references checked
Zeymer 2017[326]	Incorrect study comparison
Zhang 2009[330]	Incorrect study comparison
Zhang 2016 [329]	Incorrect intervention (very high maintanence dose of clopidogrel)
Zhang 2017[328]	Meta-analysis; references checked
Zhao 2008[331]	Incorrect study comparison
Zheng 2013[332]	Not available
Zhou 2012[333]	Systematic review; incorrect study comparison
Zhu 2015[334]	Incorrect study comparison (post-PCI administration of clopidogrel to both groups)

I.2 Excluded health economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2003 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 30: Studies excluded from the health economic review

Reference	Reason for exclusion
Davies 2013(a)[37]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing prasugrel with clopidogrel based on the same RCT[54] was available, this study was selectively excluded.
Davies 2013(b)[38]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK

Reference	Reason for exclusion
	analysis comparing prasugrel with clopidogrel based on the same RCT[54] was available, this study was selectively excluded.
De La Puente 2017[39]	Excluded as rated very serious limitations due to having a short time horizon and having unclear baseline and treatment effects. Also partially applicable, reasons include: Chilean setting may not reflect current UK NHS context.
Gasche 2013[51]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Grima 2015[55]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Henriksson 2014[57]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Liew 2013[102]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Nikolic 2013[168]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Paweska 2014[189]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Theidel 2013[267]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis comparing ticagrelor with clopidogrel based on the same RCT[125] was available, this study was selectively excluded.
Wein 2017[295]	Excluded as rated very serious limitations due to having a very short time horizon and was based on data from two trials that were not designed to compare prasugrel and clopidogrel. Also partially applicable, reasons include: German, Danish and Swiss setting may not reflect current UK NHS context.

Appendix J: Research recommendation

J.1.1 Research recommendation

What is the most effective dual anti-platelet therapy in people aged 75 and over with Acute Coronary Syndromes (ACS), who are being treated with PCI?

J.1.2 Why this is important

The evidence review for this update has found that prasugrel is the most clinical and cost effecticve agent when used with aspirin in the general ACS population being treated with PCI, particularly in STEMI. However, the summary of product characteristics (SMPC) for prasugrel states that the use of prasugrel "in patients ≥75 years of age is generally not recommended and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings." There was insufficient data available for this Guideline's evidence review to determine whether prasugrel is less effective, or even harmful in the subgroup of people aged 75 and over with ACS being treated with PCI. As NICE cannot recommend treatments outwith their SMPC, the Guideline Committee have been unable to give clear guidance as to the optimal dual anti-platelet therapy to recommend in older people.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Determining the most effective dual anti-platelet therapy in people aged 75 and over with ACS being treated with PCI, will allow this patient subgroup (who are often at the highest risk of not only death and recurrent heart attack, but also bleeding induced by therapy) to gain the most benefit from reduction in death and myocardial infarction, with least risk of suffering major bleeding.
Relevance to NICE guidance	Prasugrel has been found to be the most clinical and cost effective agent when used with aspirin in the general ACS population being treated with PCI, but its SMPC restricts its routine use in people aged 75 and over.
Relevance to the NHS	Tens of thousands of people with ACS are treated with PCI by the NHS every year, of whom a substantial proportion are aged 75 and over
National priorities	High
Current evidence base	There are no dedicated RCTs evaluating the relative clinical and cost effectiveness of clopidogrel vs prasugrel vs ticagrelor in people with ACS aged 75 and over, nor are there adequate individual patient-level data available from the individual RCTs comparing the 3 drugs to permit meta-analysis of clinical endpoints in patients aged 75 and over. The recently published POPULAR-AGE RCT (Lancet, 2020), only recruited patients with NSTEMI, and

	although it was billed as a comparison of clopidogrel, prasugrel and ticagrelor in patients aged 70 and over, only a very small proportion of patients were actually treated with prasugrel. It was published too late to be included in the evidence review for this guideline, but did appear to show that clopidogrel had equal efficacy to ticagrelor in terms of preventing MI and mortality, with less bleeding, but with so few patients included who were taking prasugrel it does not clarify its safety and efficacy in older people. Concern about use of prasugrel in older people came from the original pivotal RCT of prasugrel vs clopidogrel (TRITON, NEJM, 2007), which showed a potentially harmful excess of bleeding in people aged 75 and over with no reduction in death, MI or stroke. However, this was using the usual maintenance dose of 10mg od in all patients. More recent studies with prasugrel, including ISAR-REACT 5 (included in this evidence review), have used a reduced maintenance dose of 5mg od in this age group (in line with the UK license for prasugrel as set out in the BNF). Subgroup analysis of the just under 25% of patients in ISAR REACT-5 (982/2018) who were aged 75 or over showed a trend towards superiority of prasugrel over ticagrelor for the combined primary endpoint of death MI or stroke at 1 year in line with the overall trial results, but safety data on bleeding were not presented for this age group (although the overall trial population had numerically less bleeding woth prasugrel than ticagrelor).
Equality considerations	The strong caution against the use of prasugrel in its SmPC in people aged 75 and over, inevitably restricts the use of prasugrel this age group, thereby potentially denying older people clinical benefits of prasugrel therapy, on the basis of safety data informed by a dose of prasugrel that is no longer used in older patients.

J.1.4 Modified PICO table

Population	People with ACS aged 75 or over being treated with PCI.
Intervention	Prasugrel (5mg od maintenance dose) or Ticagrelor (90mg bd maintenance dose) in combination with aspirin as dual anti-platelet therapy
Comparator	Clopidogrel (75mg od maintenance dose) in combination with aspirin as dual anti-platelet therapy
Outcome	Death, MI, stroke, major bleeding and Quality of Life at 1 year

Study design	RCT