National Institute for Health and Care Excellence

Consultation

Acute coronary syndrome

[G] Combination therapy

NICE guideline

Intervention evidence review

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

Disclaimer

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1 Combination therapy

1.1 Review question: What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an ACS and a separate indication for anticoagulation?

1.2 Introduction

The roles of anti-platelet and anticoagulant therapy in the short and long-term management of acute coronary syndromes (ACS) are relatively well established, with both having a role in the acute in-hospital treatment phase but anti-platelet therapy alone generally being recommended after discharge. However, registry data indicate that a modest proportion of patients suffering ACS will also have a co-existing medical condition (e.g. atrial fibrillation (AF), venous thrombo-embolism, or mechanical heart valve) for which long-term anti-coagulant therapy is usually indicated.

Prescribing a clinically and cost effective combination of oral anti-coagulant and anti-platelet therapy in this patient group has been the subject of debate due to potential increased risks of bleeding not only with newer anti-platelet drugs (ticagrelor and prasugrel) but also when anti-platelet and anti-coagulant therapy are co-prescribed long-term. It is also unclear how an ACS and addition of anti-platelet therapy may change the clinical and cost-effectiveness of the newer direct oral anti-coagulants (dabigatran, rivaroxaban, apixaban and edoxaban) which are increasingly prescribed in patients with AF.

NICE CG 172 recommends the combination of warfarin anti-coagulation with clopidogrel or aspirin as anti-platelet therapy for most ACS patients with an indication for anti-coagulation, and specifically recommends against combining newer anti-platelet and direct oral anti-coagulant therapies. The publication of new randomised trial data evaluating direct oral anti-coagulants in ACS and coronary stent patients means that existing guidance may need to be updated, and this current review was performed to examine that possibility.

It should be noted that this review addresses only the situations in which anti-coagulants are used for a second condition which co-exists with ACS, in contrast to NICE TA335 which recommends rivaroxaban as an option, in combination with aspirin plus clopidogrel or aspirin alone, for preventing atherothrombotic events in selected people with an ACS.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	• Adults (≥ 18 years) who have had ACS and a comorbid condition needing oral anticoagulation. The following groups may be included: • Patients with mechanical valve replacements • Patients with VTE needing continuing treatment • Patients who have left ventricular thrombus • Patients with atrial fibrillation (AF) who have had an MI and are taking

	anticoagulant agents • Mixed populations (ACS and stable) may be included if > 60% ACS • Papers including between 50-60% ACS may be included and downgraded for indirectness except for bleeding outcomes as these are not likely to be different in stable and unstable patients
Interventions	**Intervention = Post discharge treatment** (may be initiated in hospital but should not be stopped before discharge). • Dual antiplatelet therapy + warfarin • Dual antiplatelet therapy + rivaroaiban • Dual antiplatelet therapy + dabigatran • Dual antiplatelet therapy + apixaban • Dual antiplatelet therapy + edoxaban • Asprin + apixaban • Aspirin + warfarin • Aspirin + rivaroxaban • Aspirin + dabigatran • Aspirin + edoxaban • Clopidogrel/prasugrel/ticagrelor + warfarin • Clopidogrel/prasugrel/ticagrelor + rivaroxaban • Clopidogrel/prasugrel/ticagrelor + dabigatran • Clopidogrel/prasugrel/ticagrelor + apixaban • Clopidogrel/prasugrel/ticagrelor + edoxaban Note Dual antiplatelet therapy = aspirin + clopidogrel/ticagrelor/prasugrel **Duration** Studies with durations of follow up of up to 2 years will be included in the review. The duration of treatment and follow up will be considered when evaluating the benefits and risks for these therapies:
Comparisons	**Comparison** • Dual antiplatelet therapy alone • Warfarin alone • Rivaroxaban alone • Dabigatran alone • apixaban alone • Aspirin alone • Clopidogrel/prasugrel/ticagrelor alone • Edoxaban
Outcomes	**CRITICAL** • All cause mortality - short term (≤30 days) • All cause mortality- intermediate term (up to 1 year) • All cause mortality- long term (>1 year) • Myocardial re-infarction - short term (≤30 days) • Myocardial re-infarction - intermediate term (up to 1 year)

	• Myocardial re-infarction - short term (≤30 days) • stroke - short term (≤30 days) • stroke - long term (>1 year) • stroke - short term (≤30 days) • Complications related to bleeding short term (≤30 days), intermediate term (up to 1 year), and long term (>1 year) including haemorrhagic stroke –(access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: o BARC o Author's definition o TIMI o GUSTO Where possible, bleeding outcomes will be categorised into: o Major bleeding (including BARC 3-5 and as reported by author) o Minor bleeding (including BARC 2, TIMI and as reported by author). – 1 year • Health-related quality of life including EQ5D and SF-36. All data for the stated quality of life measures will be collected. Only overall scores will be reported for meta-analysis and GRADE. **IMPORTANT** • withdrawal of study drug due to any side effect • Probable and/or definite stent thrombosis at 1 year
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.[70] Methods specific to this review question are described in the review protocol in Appendix A:

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

1.5 Clinical evidence

1.5.1 Included studies

Four studies (13 papers) were included in the review.[3, 19, 20, 23, 35-37, 43, 49, 50, 60, 62, 75, 88] Evidence from these studies is summarised in the clinical evidence summary below (Table 2).

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 F:

1.5.2 Excluded studies

See the excluded studies list in Appendix J:

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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
REDUAL Cannon 2016[20] Cannon 2017[19] Oldgren 2019[75]	Warfarin (INR 2-3) plus a P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) plus aspirin (≤100 mg daily) Dabigatran (110 mg twice daily) plus a P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily)	2725 people with atrial fibrillation who had undergone PCI PCI population who also had AF Stable angina: 43%; ACS: 50%; other: 6%	Death Myocardial infarction Stroke Definite stent thrombosis Complications related to bleeding - TIMI major bleeding - TIMI major or minor bleeding - Intracranial haemorrhage - Total bleeding	Most of the patients received clopidogrel; only 12.0% received ticagrelor
PIONEER AF PCI Gibson 2016[36], Gibson 2015[35], Gibson 2017[37], Kerneis 2018[49] Kerneis 2019[50] Chi 2018[23]	Rivaroxaban (15 mg once daily) plus clopidogrel (75 mg once daily) (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) Rivaroxaban (2.5 mg twice daily) plus clopidogrel (75 mg once daily) (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) plus aspirin (75 to 100 mg per day)	2124 people with paroxysmal, persistent, or permanent non-valvular atrial fibrillation who had undergone PCI with stenting NSTEMI: 18%; STEMI: 12%; unstable angina: 22%	Death Myocardial infarction Stroke Stent thrombosis Complications related to bleeding - Major bleeding - Minor bleeding - Bleeding requiring medical attention - Clinically significant bleeding	Approximately 94% of participants had clopidogrel

Study	Intervention and comparison	Population	Outcomes	Comments
	Warfarin (INR 2-3) plus clopidogrel (75 mg once daily) (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants+ aspirin) plus aspirin (75 to 100 mg per day)			
AUGUSTUS Lopes 2018[62] Lopes 2019[60] Haller 2019[43]	Apixaban plus aspirin plus P2Y12 inhibitor Warfarin plus aspirin plus P2Y12 inhibitor Apixaban plus P2Y12 inhibitor plus placebo Warfarin plus P2Y12 inhibitor plus placebo The P2Y12 inhibitor was clopidogrel in >90% of participants	4614 people with atrial fibrillation who had an acute coronary syndrome or had undergone PCI	Death Stroke Myocardial infarction Complications related to bleeding - Intracranial haemorrhage - GUSTO severe bleeding - GUSTO moderate bleeding - TIMI major bleeding - TIMI minor bleeding	
ENTRUST-AF PCI Vranckx 2019[88]	Edoxaban (60mg once daily) plus a P2Y12 inhibitor (clopidogrel 75mg once daily) for 12 months Vitamin K antagonist (INR 2-3) plus a P2Y12 inhibitor (clopidogrel 75mg once daily) plus aspirin (100mg once daily	1506 people with atrial fibrillation requiring oral anticoagulation who were at least 18 years old and had successful PCI for stable coronary artery disease (48%) or ACS (52%)	Death Stroke Myocardial infarction Stent thrombosis Complications related to bleeding - Major or clinically relevant non-major bleeding	Not clear which VKA used

Study	Intervention and comparison	Population	Outcomes	Comments
	for 1-12 months)		- Major bleeding - Intracranial haemorrhage	

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: Warfarin + clopidogrel + aspirin versus warfarin + clopidogrel

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
All cause mortality - 6 months	2308 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.85 (0.54 to 1.33)	35 per 1000	5 fewer per 1000 (from 16 fewer to 12 more)
Myocardial infarction - 6 months	2308 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.74 (0.48 to 1.14)	40 per 1000	10 fewer per 1000 (from 21 fewer to 6 more)
Stroke - 6 months	2308 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.86 (0.4 to 1.85)	12 per 1000	2 fewer per 1000 (from 7 fewer to 10 more)
Any stent thrombosis - 6 months	2308 (1 study)	⨁⨁⨀⨀ LOW1 due to imprecision	RR 0.63 (0.31 to 1.3)	17 per 1000	6 fewer per 1000 (from 12 fewer to 5 more)
Complications relating to bleeding - TIMI major	2249	⨁⨁⨁⨀	RR 1.62	16 per 1000	10 more per 1000

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
6 months	(1 study)	MODERATE[1] due to imprecision	(0.9 to 2.89)		(from 2 fewer to 30 more)
Complications relating to bleeding - TIMI major and minor - 6 months	2249 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.57 (1.12 to 2.21)	45 per 1000	26 more per 1000 (from 5 more to 54 more)
Complications relating to bleeding - Intracranial haemorrhage - 6 months	2249 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.5 (0.15 to 1.66)	7 per 1000	3 fewer per 1000 (from 6 fewer to 5 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 4: Clinical evidence summary: Warfarin + clopidogrel + aspirin versus dabigatran + clopidogrel

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with dabigatran + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
All-cause mortality - 14 months	1962 (1 study)	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.6 to 1.27)	56 per 1000	7 fewer per 1000 (from 22 fewer to 15 more)
Myocardial infarction - 14 months	1962 (1 study)	⨁⨁⨀⨀ LOW[1,2] due to risk of bias, imprecision	RR 0.66 (0.42 to 1.04)	45 per 1000	15 fewer per 1000 (from 26 fewer to 2 more)
Stroke - 14 months	1962 (1 study)	⨁⨀⨀⨀ VERY LOW[1,2]	RR 0.76 (0.37 to	17 per 1000	4 fewer per 1000 (from 11 fewer to 10 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with dabigatran + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
		due to risk of bias, imprecision	1.57)		
Definite stent thrombosis - 14 months	1962 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.23 to 1.25)	15 per 1000	7 fewer per 1000 (from 12 fewer to 4 more)
Complications relating to bleeding - Intracranial haemorrhage - 14 months	1962 (1 study)	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 3.33 (0.92 to 12.08)	3 per 1000	7 more per 1000 (from 0 fewer to 33 more)
Complications relating to bleeding - TIMI major bleeding - 14 months	1962 (1 study)	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	RR 2.64 (1.44 to 4.86)	14 per 1000	23 more per 1000 (from 6 more to 54 more)
Complications relating to bleeding - TIMI major and minor bleeding 14 months	1962 (1 study)	⊕⊕⊕⊖ MODERATE[1] due to risk of bias	RR 2.38 (1.56 to 3.64)	30 per 1000	41 more per 1000 (from 17 more to 79 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 once for serious imprecision, and twice for very serious imprecision

Table 5: Clinical evidence summary: Rivaroxaban (2.5 mg bd) + clopidogrel + aspirin versus rivaroxaban (15 mg od) + clopidogrel

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with rivaroxaban + clopidogrel	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with rivaroxaban + clopidogrel	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)
	(1 study)	VERY LOW[1,2] due to risk of bias, imprecision	1.05 (0.53 to 2.06)	23 per 1000	1 more per 1000 (from 11 fewer to 24 more)
Myocardial infarction - 12 months	1398 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.88 (0.46 to 1.68)	27 per 1000	3 fewer per 1000 (from 15 fewer to 18 more)
Stroke - 12 months	1398 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.23 (0.49 to 3.1)	12 per 1000	3 more per 1000 (from 6 fewer to 25 more)
Stent thrombosis - 12 months	1398 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.18 (0.36 to 3.86)	7 per 1000	1 more per 1000 (from 4 fewer to 20 more)
Complications relating to bleeding - Bleeding requiring medical attention - 12 months	1402 (1 study)	⊕⊕⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.08 (0.83 to 1.4)	134 per 1000	11 more per 1000 (from 23 fewer to 54 more)
Complications relating to bleeding - Major bleeding- 12 months	1402 (1 study)	⊕⊖⊖⊖ VERY LOW[1,2] due to risk of bias,	RR 0.85 (0.39 to 1.81)	20 per 1000	3 fewer per 1000 (from 12 fewer to 16 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with rivaroxaban + clopidogrel	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)
		imprecision			
Complications relating to bleeding - Minor bleeding 12 months	1402 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.99 (0.35 to 2.8)	10 per 1000	0 fewer per 1000 (from 7 fewer to 18 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

Table 6: Clinical evidence summary: Rivaroxaban (2.5 mg bd) + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel + aspirin	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)
All-cause mortality- 12 months	1399 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of	RR 1.29 (0.63 to	19 per 1000	5 more per 1000 (from 7 fewer to 31 more)

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel + aspirin	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)
		bias, imprecision	2.64)		
Myocardial infarction - 12 months	1399 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.8 (0.43 to 1.5)	30 per 1000	6 fewer per 1000 (from 17 fewer to 15 more)
Stroke - 12 months	1399 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.41 (0.54 to 3.68)	10 per 1000	4 more per 1000 (from 5 fewer to 27 more)
Stent thrombosis - 12 months	1398 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.48 (0.42 to 5.22)	6 per 1000	3 more per 1000 (from 3 fewer to 25 more)
Complications relating to bleeding - Bleeding requiring medical attention - 12 months	1403 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 0.72 (0.57 to 0.91)	199 per 1000	56 fewer per 1000 (from 18 fewer to 86 fewer)
Complications relating to bleeding - Major bleeding 12 months	1403 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias,	RR 0.59 (0.29 to 1.2)	29 per 1000	12 fewer per 1000 (from 21 fewer to 6 more)

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel + aspirin	Risk difference with Rivaroxaban + clopidogrel + aspirin (95% CI)
		imprecision			
Complications relating to bleeding - Minor bleeding 12 months	1403 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.53 (0.21 to 1.32)	19 per 1000	9 fewer per 1000 (from 15 fewer to 6 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

Table 7: Clinical evidence summary: Warfarin + clopidogrel + aspirin versus Rivaroxaban (15 mg od)+ clopidogrel

Outcomes	No of	Quality of the	Relativ	Anticipated absolute effects

Follow up	Participants (studies)	evidence (GRADE)	e effect (95% CI)	Risk with Rivaroxaban + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
All-cause mortality - 12 months	1389 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.81 (0.39 to 1.67)	23 per 1000	4 fewer per 1000 (from 14 fewer to 15 more)
Myocardial infarction - 12 months	1389 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.1 (0.6 to 2.03)	27 per 1000	3 more per 1000 (from 11 fewer to 28 more)
Stroke - 12 months	1389 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.32 to 2.4)	12 per 1000	2 fewer per 1000 (from 8 fewer to 17 more)
Stent thrombosis - 12 months	1389 (1 study) 12 months	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.8 (0.22 to 2.96)	7 per 1000	1 fewer per 1000 (from 5 fewer to 14 more)
Complications related to bleeding - Bleeding requiring medical attention - 12 months	1393 (1 study)	⨁⨁⊖⊖ LOW[1,2] due to risk of bias, imprecision	RR 1.49 (1.17 to 1.9)	134 per 1000	66 more per 1000 (from 23 more to 121 more)
Complications related to bleeding - Major bleeding 12 months	1393 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias,	RR 1.43 (0.73 to 2.8)	20 per 1000	9 more per 1000 (from 5 fewer to 36 more)

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Rivaroxaban + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
		imprecision			
Complications related to bleeding - Minor bleeding 12 months	1393 (1 study)	⨁⊖⊖⊖ VERY LOW[1,2] due to risk of bias, imprecision	RR 1.85 (0.74 to 4.62)	10 per 1000	9 more per 1000 (from 3 fewer to 36 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

Table 8: Clinical evidence summary: Apixaban + clopidogrel + aspirin versus apixaban + clopidogrel

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with apixaban + clopidogrel	Risk difference with Apixaban + clopidogrel + aspirin (95% CI)
All-cause mortality - 6 months	2306 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.97 (0.63 to 1.51)	34 per 1000	1 fewer per 1000 (from 13 fewer to 17 more)
Myocardial infarction - 6 months	2306 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.89 (0.57 to 1.41)	33 per 1000	4 fewer per 1000 (from 14 fewer to 14 more)

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with apixaban + clopidogrel	Risk difference with Apixaban + clopidogrel + aspirin (95% CI)
	(1 study)	LOW[1] due to imprecision	(0.52 to 4.88)	4 per 1000	2 more per 1000 (from 2 fewer to 16 more)
Stent thrombosis - 6 months	2306 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.52 (0.25 to 1.08)	18 per 1000	9 fewer per 1000 (from 13 fewer to 1 more)
Complications relating to bleeding - TIMI major bleeding - 6 months	2288 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.92 (0.99 to 3.73)	11 per 1000	10 more per 1000 (from 0 fewer to 30 more)
Complications relating to bleeding - TIMI major and minor bleeding - 6 months	2288 (1 study)	⨁⨁⨁⨁ HIGH	RR 2 (1.32 to 3.03)	28 per 1000	28 more per 1000 (from 9 more to 57 more)
Complications relating to bleeding - Intracranial haemorrhage - 6 months	2288 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 3.99 (0.45 to 35.67)	Moderate	
				1 per 1000	3 more per 1000 (from 1 fewer to 35 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 9: Clinical evidence summary: Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel + aspirin	Risk difference with Apixaban + clopidogrel + aspirin (95% CI)
All-cause mortality - 6 months	2307	⨁⨁⨀⨀	RR 1.12	30 per 1000	4 more per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel + aspirin	Risk difference with Apixaban + clopidogrel + aspirin (95% CI)
	(1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	(0.71 to 1.76)		(from 9 fewer to 23 more)
Myocardial infarction - 6 months	2307 (1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 1 (0.63 to 1.6)	30 per 1000	0 fewer per 1000 (from 11 fewer to 18 more)
Stroke - 6 months	2307 (1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 0.67 (0.27 to 1.63)	Moderate	
				10 per 1000	3 fewer per 1000 (from 7 fewer to 6 more)
Any stent thrombosis - 6 months	2307 (1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 0.92 (0.41 to 2.07)	10 per 1000	1 fewer per 1000 (from 6 fewer to 11 more)
Complications related to bleeding - TIMI major bleeding - 6 months	2268 (1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 0.85 (0.5 to 1.43)	26 per 1000	4 fewer per 1000 (from 13 fewer to 11 more)
Complications related to bleeding - TIMI minor bleeding - 6 months	2268 (1 study)	⊕⊕⊕⊖ MODERATE[1] due to imprecision	RR 0.78 (0.57 to 1.08)	71 per 1000	16 fewer per 1000 (from 31 fewer to 6 more)
Complications related to bleeding - Intracranial haemorrhage - 6 months	2268 (1 study)	⊕⊕⊖⊖ LOW[1] due to imprecision	RR 0.98 (0.25 to 3.91)	4 per 1000	0 fewer per 1000 (from 3 fewer to 12 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 10: Clinical evidence summary: Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel

Outcomes Follow up	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel	Risk difference with Apixaban + clopidogrel + aspirin (95% CI)
All-cause mortality - 6 months	2307 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.95 (0.61 to 1.47)	35 per 1000	2 fewer per 1000 (from 14 fewer to 16 more)
Myocardial infarction- 6 months	2307 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.74 (0.48 to 1.14)	40 per 1000	10 fewer per 1000 (from 21 fewer to 6 more)
Stroke- 6 months	2307 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.57 (0.24 to 1.36)	12 per 1000	5 fewer per 1000 (from 9 fewer to 4 more)
Any stent thrombosis- 6 months	2307 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 0.58 (0.28 to 1.21)	17 per 1000	7 fewer per 1000 (from 12 fewer to 4 more)
Complications related to bleeding - TIMI major bleeding- 6 months	2271 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 1.37 (0.75 to 2.49)	16 per 1000	6 more per 1000 (from 4 fewer to 24 more)
Complications related to bleeding - TIMI major and minor bleeding 6 months	2271 (1 study)	⨁⨁⨁⊖ MODERATE[1] due to imprecision	RR 1.23 (0.86 to 1.77)	45 per 1000	10 more per 1000 (from 6 fewer to 35 more)
Complications related to bleeding - Intracranial haemorrhage 6 months	2271 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.98 (0.25 to 3.92)	4 per 1000	0 fewer per 1000 (from 3 fewer to 12 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 11: Clinical evidence summary: Warfarin + clopidogrel + aspirin versus apixaban + clopidogrel

Outcomes	No of	Quality of the	Relativ	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	e effect (95% CI)	Risk with apixaban + clopidogrel	Risk difference with Warfarin + clopidogrel + aspirin (95% CI)
All-cause mortality- 6 months	2307 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.02 (0.66 to 1.58)	34 per 1000	1 more per 1000 (from 12 fewer to 20 more)
Myocardial infarction - 6 months	2307 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.35 (0.87 to 2.09)	30 per 1000	11 more per 1000 (from 4 fewer to 33 more)
Stroke- 6 months	2307 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.75 (0.74 to 4.15)	7 per 1000	5 more per 1000 (from 2 fewer to 22 more)
Any stent thrombosis -6 months	2307 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.73 (0.82 to 3.61)	10 per 1000	7 more per 1000 (from 2 fewer to 26 more)
Complications related to bleeding - TIMI major bleeding - 6 months	2269 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.41 (0.69 to 2.85)	11 per 1000	5 more per 1000 (from 3 fewer to 20 more)
Complications related to bleeding - TIMI major and minor bleeding -6 months	2269 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.62 (1.05 to 2.5)	28 per 1000	17 more per 1000 (from 1 more to 42 more)
Complications related to bleeding - Intracranial haemorrhage- 6 months	2269 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 8.12 (1.02 to 64.82)	1 per 1000	7 more per 1000 (from 0 more to 64 more)

1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 12: Clinical evidence summary: Apixaban + clopidogrel versus warfarin + clopidogrel

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel	Risk difference with Apixaban + clopidogrel (95% CI)
All-cause mortality - 6 months	2307 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.98 (0.63 to 1.51)	35 per 1000	1 fewer per 1000 (from 13 fewer to 18 more)
Myocardial infarction- 6 months	2307 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.83 (0.54 to 1.26)	40 per 1000	7 fewer per 1000 (from 18 fewer to 10 more)
Stroke- 6 months	2307 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.36 (0.13 to 0.99)	12 per 1000	8 fewer per 1000 (from 0 fewer to 10 fewer)
Any stent thrombosis- 6 months	2307 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.11 (0.6 to 2.05)	17 per 1000	2 more per 1000 (from 7 fewer to 18 more)
Complications related to bleeding - TIMI major bleeding - 6 months	2269 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.71 (0.35 to 1.45)	16 per 1000	5 fewer per 1000 (from 10 fewer to 7 more)
Complications related to bleeding - TIMI major and minor bleeding - 6 months	2269 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 0.62 (0.4 to 0.95)	45 per 1000	17 fewer per 1000 (from 2 fewer to 27 fewer)
Complications related to bleeding - Intracranial haemorrhage- 6 months	2269 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to	RR 0.12 (0.02 to 0.98)	7 per 1000	6 fewer per 1000 (from 0 fewer to 7 fewer)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with warfarin + clopidogrel	Risk difference with Apixaban + clopidogrel (95% CI)
		imprecision			
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 13: Clinical evidence summary: edoxaban + clopidogrel versus VKA + clopidogrel + aspirin

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA + clopidogrel + aspirin	Risk difference with Edoxaban + clopidogrel (95% CI)
All-cause mortality -12 months	1506 (1 study)	⨁⨁⨁⨀ MODERATE[1] due to imprecision	RR 1.25 (0.82 to 1.9)	49 per 1000	12 more per 1000 (from 9 fewer to 44 more)
Stroke- 12 months	1506 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 0.84 (0.36 to 1.93)	16 per 1000	3 fewer per 1000 (from 10 fewer to 15 more)
Myocardial infarction- 12 months	1506 (1 study)	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.27 (0.74 to 2.17)	31 per 1000	8 more per 1000 (from 8 fewer to 36 more)
Stent thrombosis - 12 months	1506 (1 study) 12 months	⨁⨁⨀⨀ LOW[1] due to imprecision	RR 1.31 (0.58 to 2.96)	13 per 1000	4 more per 1000 (from 5 fewer to 25 more)
Complications related to bleeding - Major or clinically relevant	1506	⨁⨁⨁⨀	RR	201 per 1000	30 fewer per 1000

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with VKA + clopidogrel + aspirin	Risk difference with Edoxaban + clopidogrel (95% CI)
non-major bleeding (ISTH)- 12 months	(1 study)	MODERATE[1] due to imprecision	0.85 (0.68 to 1.05)		(from 64 fewer to 10 more)
Complications related to bleeding - Major bleeding (ISTH)- 12 months	1506 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.94 (0.64 to 1.4)	64 per 1000	4 fewer per 1000 (from 23 fewer to 26 more)
Complications related to bleeding - Intracranial haemorrhage 12 months	1506 (1 study)	⨁⨁⊖⊖ LOW[1] due to imprecision	RR 0.45 (0.14 to 1.44)	12 per 1000	7 fewer per 1000 (from 10 fewer to 5 more)
1 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

See Appendix F: for full GRADE tables.

1.6 Economic evidence

1.6.1 Included studies

No health economic studies were included.

1.6.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

1.6.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.6.4 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 14: UK costs of anticoagulants and antiplatelets

Drug	Preparation	Daily dose[(a)]	Cost per day	Cost per year
Anticoagulants				
Apixaban	Tablet	2.5mg twice daily	£1.90	£693.50
		5mg twice daily	£1.90	£693.50
Dabigatran	Capsule	110mg twice daily	£1.70	£620.50
		150mg twice daily	£1.70	£620.50
Edoxaban	Tablet	30mg once daily	£1.75	£638.75
		60mg once daily	£1.75	£638.75
Rivaroxaban	Tablet	2.5mg twice daily	£1.80	£657.00
		10mg once daily	£1.80	£657.00
		15mg once daily	£1.93	£703.93
		20mg once daily	£1.80	£657.00
Warfarin	Tablet	3mg once daily	£0.01	£4.82
		5mg once daily	£0.02	£5.48
Antiplatelets[(b)]				
Aspirin	Tablet	75mg once daily	£0.02	£7.95
Clopidogrel	Tablet	75mg once daily	£0.05	£16.95
Prasugrel	Tablet	5mg once daily	£1.39	£507.22
		10mg once daily	£1.39	£507.22
Ticagrelor	Tablet	90mg twice daily	£1.95	£711.75

Source: NHS Drug Tariff prices obtained from the BNF; accessed September 2018[48]
(a) Dose obtained from the BNF
(b) Cost of antiplatelets do not include loading dose

1.7 Evidence statements

1.7.1 Clinical evidence statements

Warfarin + clopidogrel + aspirin compared to warfarin + clopidogrel

- There was a clinically important benefit of the combination of warfarin + clopidogrel + aspirin compared to warfarin + clopidogrel for all-cause mortality and myocardial infarction (2038 participants in 1 study, low and moderate quality evidence respectively).
- There was a clinically important harm in TIMI major and minor bleeding when using a combination of warfarin + clopidogrel + aspirin compared to warfarin + clopidogrel (2249 participants in 1 study, moderate quality evidence).
- There was no clinically important difference between warfarin + clopidogrel + aspirin compared to warfarin + clopidogrel alone for any stent thrombosis, stroke (2038 participants in 1 study, low quality evidence), TIMI major bleeding and intracranial haemorrhage (2249 participants in 1 study, low and moderate quality evidence respectively).

Warfarin + clopidogrel + aspirin compared to dabigatran + clopidogrel

- There was a clinically important benefit of the combination of warfarin + clopidogrel + aspirin compared to dabigatran + clopidogrel for all-cause mortality and myocardial infarction (1962 participants in 1 study, very low and low quality evidence respectively)
- There was a clinically important harm in TIMI major bleeding, and TIMI major and minor bleeding when using warfarin + clopidogrel + aspirin compared to dabigatran + clopidogrel (1962 participants in 1 study, moderate quality evidence).
- There was no clinically important difference in stroke, definite stent thrombosis, and complications related to bleeding in terms of intracranial haemorrhage (1962 participants in 1 study, very low to low quality evidence).

Rivaroxaban (2.5 mg bd) + clopidogrel + aspirin compared to rivaroxaban (15 mg od) + clopidogrel

- There was a clinically important harm in all-cause mortality at 12 months (1398 participants in 1 study, very low quality evidence) when using rivaroxaban + clopidogrel +_aspirin compared to rivaroxaban + clopidogrel
- There was no clinically important difference in myocardial infarction, stroke, stent thrombosis (1398 participants in 1 study, very low quality evidence) and bleeding complications requiring medical attention, major bleeding, and minor bleeding (1402 participants in 1 study, very low quality evidence).

Rivaroxaban (2.5 mg bd) + clopidogrel + aspirin compared to warfarin + clopidogrel + aspirin

- There was a clinically important benefit of rivaroxaban (2.5 mg bd) + clopidogrel + aspirin compared to warfarin + clopidogrel + aspirin for bleeding complications requiring medical attention (1403 participants in 1 study, very low quality evidence).
- There was a clinically important harm in all-cause mortality when using rivaroxaban (2.5 mg bd) + clopidogrel + aspirin compared to warfarin + clopidogrel + aspirin (1399 participants in 1 study, very low quality evidence).
- There was no clinically important difference in myocardial infarction, stroke, stent thrombosis (1399 participants in 1 study, very low quality evidence) and major and minor bleeding (1403 participants in 1 study, low and very low quality evidence respectively).

Warfarin + clopidogrel + aspirin compared to Rivaroxaban (15 mg od)+ clopidogrel

- There was a clinically important benefit of warfarin + clopidogrel + aspirin compared rivaroxaban (15 mg od) + clopidogrel for all-cause mortality (1389 participants in 1 study, very low quality evidence).
- There was a clinically important harm in bleeding requiring medical attention when using warfarin + clopidogrel + aspirin compared to rivaroxaban + clopidogrel (1393 participants in 1 study, low quality evidence).
- There was no clinically important difference in myocardial infarction, stroke, stent thrombosis, (1389 participants in 1 study, very low quality evidence), major and minor bleeding (1393 participants in 1 study, very low quality evidence).

Apixaban + clopidogrel + aspirin compared to apixaban + clopidogrel

- There was a clinically important benefit of apixaban + clopidogrel + aspirin compared to apixaban + clopidogrel for all-cause mortality (2306 participants in 1 study, low quality evidence).
- There was a clinically important harm in TIMI major and minor bleeding when using apixaban + clopidogrel + aspirin compared to apixaban + clopidogrel (2288 participants in 1 study, high quality evidence).
- There was no clinically important difference in myocardial infarction, stroke, stent thrombosis (2306 participants in 1 study, low to moderate quality evidence) and in TIMI major bleeding, and intracranial haemorrhage (2288 participants in 1 study, high and low quality evidence respectively).

Apixaban + clopidogrel + aspirin compared to warfarin + clopidogrel + aspirin

- There was a clinically important harm in all-cause mortality when using apixaban + clopidogrel + aspirin compared to warfarin + clopidogrel + aspirin (2307 participants in 1 study, low quality evidence).
- There was no clinically important difference in myocardial infarction, stroke, any stent thrombosis (2307 participants in 1 study, low quality evidence) and in TIMI major bleeding, TIMI major and minor bleeding, and intracranial haemorrhage (2268 participants in 1 study, low quality evidence).

Apixaban + clopidogrel + aspirin compared to warfarin + clopidogrel

- There was a clinically important benefit of apixaban + clopidogrel + aspirin compared to warfarin + clopidogrel for all-cause mortality and myocardial infarction (2307 participants in 1 study, low and moderate quality evidence respectively).
- There was no clinically important difference between apixaban + clopidogrel + aspirin and warfarin + clopidogrel for stroke, any stent thrombosis (2307 participants in 1 study, moderate quality evidence) and in TIMI major bleeding, TIMI major and minor bleeding, and intracranial haemorrhage (2271 participants in 1 study, low to moderate quality evidence).

Warfarin + clopidogrel + aspirin compared to apixaban + clopidogrel

- There was a clinically important harm in all-cause mortality and myocardial infarction when using warfarin + clopidogrel + aspirin compared to apixaban + clopidogrel (2307 participants in 1 study, low and moderate quality evidence respectively).
- There was no clinically important difference in stroke, any stent thrombosis (2307 participants in 1 study, low and moderate quality evidence respectively) and in TIMI major bleeding, TIMI major and minor bleeding, and intracranial haemorrhage (2269 participants in 1 study, low to moderate quality evidence).

Apixaban + clopidogrel compared to warfarin + clopidogrel

- There was a clinically important benefit of apixaban + clopidogrel compared to warfarin + clopidogrel for all-cause mortality (2307 participants in 1 study, low quality evidence).
- There was no clinically important difference in myocardial infarction, stroke, any stent thrombosis (2307 participants in 1 study, low to moderate quality evidence), TIMI major bleeding, TIMI major and minor bleeding, and intracranial haemorrhage (2269 participants in 1 study, low to moderate quality evidence).

Edoxaban + clopidogrel compared to VKA + clopidogrel + aspirin

- There was a clinically important benefit of edoxaban + clopidogrel versus VKA + clopidogrel + aspirin in major or clinically relevant non-major bleeding (1506 participants in 1 study, moderate quality evidence).
- There was a clinically important harm in all-cause mortality when using edoxaban + clopidogrel versus VKA + clopidogrel + aspirin (1506 participants in 1 study, moderate and low quality evidence respectively).
- There was no clinically important difference in stroke, myocardial infarction, stent thrombosis, and all bleeding outcomes including intracranial haemorrhage (1506 participants in 1 study, low to moderate quality evidence).

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

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 were all-cause mortality, myocardial re-infarction, stroke and complications related to bleeding, in the short term (≤30 days), intermediate term (up to 1 year) and long term (>1 year). Health related quality of life was also considered critical for decision making.

Withdrawal of study drug due to any side effect and stent thrombosis were considered important outcomes for decision making.

1.8.1.2 The quality of the evidence

Four randomised controlled trials were included in the review. One study (REDUAL) compared triple therapy with warfarin, clopidogrel and aspirin to DAPT with dabigatran and clopidogrel. The second study (PIONEER AF-PCI) compared three different treatment strategies: low dose rivaroxaban (15 mg once daily) plus clopidogrel, a very low dose rivaroxaban (2.5 mg twice daily) plus clopidogrel and aspirin, and triple therapy with warfarin, clopidogrel and aspirin. The third trial (AUGUSTUS) was a 2 x 2 factorial trial which compared apixaban with warfarin and aspirin with placebo and therefore provided several comparisons relevant to our review. This trial did not report the data for all the comparison arms that were relevant to our review and we were initially unable to obtain the raw data for this trial to be included. However, a network meta-analysis was later published by the same authors and this was used as the source of the raw data for the AUGUSTUS trial within this review. The fourth trial (ENTRUST PCI) compared edoxaban plus clopidogrel to triple therapy with a vitamin K antagonist (VKA) and aspirin. This study did not specify which VKA

was used but the committee agreed that as this was a very recent study, the VKA was likely to be warfarin.

From the outset, the committee did not wish to analyse the data grouped by the different classes of drugs. The aim was to make recommendations on specific drug combinations and therefore each comparison was analysed separately.

GRADE assessments across all outcomes ranged from very low to high. This was mainly due to risk of bias and imprecision.

There was no evidence available for any of the outcomes in the short term (≤30 days), nor of health related quality of life at any time point.

1.8.13 Benefits and harms

The committee agreed that when using triple therapy there was a general trend towards a reduction in mortality and MI, but no firm conclusion could be drawn because of inconsistency between studies and wide confidence intervals. Moreover, these potential benefits needed to be balanced against the clinically important increase in bleeding rates when using triple therapy. This pattern of results was seen in the study that used triple therapy with an unspecified VKA compared to dual therapy with edoxaban plus clopidogrel, and in the arms of the AUGUSTUS study in which triple therapy comprising apixaban, clopidogrel and aspirin was compared to dual therapy with either apixaban or warfarin combined with clopidogrel. However, in AUGUSTUS, triple therapy with warfarin combined with clopidogrel and aspirin did not reduce mortality compared to dual therapy with apixaban plus clopidogrel. In the PIONEER study the differences between triple therapy with rivaroxaban, clopidogrel and aspirin versus dual therapy without aspirin were small and in opposite directions for mortality and myocardial infarction, but again there was an increase in bleeding complications with triple therapy even though the dose of rivaroxaban was lower in this arm of the study. Overall the increase in bleeding risk with triple therapy was more consistent and larger than the benefit in reduction of mortality or MI, although the committee noted that there was no short-term data and they could not rule out a possible role for triple therapy in the first few weeks after presenting with ACS.

There are few opportunities in these data to directly compare newer anticoagulants with warfarin, but 2 arms of the AUGUSTUS study allow this. Triple therapy with apixaban, clopidogrel and aspirin led to slightly worse mortality than triple therapy with warfarin, but all other outcomes favoured apixaban; and when dual therapy with apixaban plus clopidogrel was compared to dual therapy using warfarin all clinical outcomes favoured apixaban. The differences were mostly relatively small, but more likely to be significant when considering bleeding complications which were less with apixaban. In the PIONEER study the combination of rivaroxaban, clopidogrel and aspirin was compared to triple therapy with warfarin. All-cause mortality, stroke and stent thrombosis were higher in the rivaroxaban arm, but risk of myocardial infarction and bleeding complications were lower, the latter significantly so. The dose of rivaroxaban used in this study was lower than that recommended for treating conditions such as atrial fibrillation or deep venous thrombosis, and the committee took this into account when considering the results.

There were no direct comparisons between any of the anticoagulant drugs other than those with warfarin.

Whilst reviewing the pairwise outcome data, the committee found it difficult to reach an over-arching conclusion about the most clinically effective treatment/s. The committee considered the proposal of conducting network meta-analyses (NMAs) of this evidence review to inform decision-making. Traditionally, an NMA can provide some clarity around the relative effects for treatments within a network and aid decision-making. However, this can be limited if there are few studies included in an NMA, leading to potential uncertainty in the results. This was the case with the NMAs that were conducted for the outcomes: all-cause mortality,

myocardial infarction and major bleeding (see further details in Appendix G). There is a lot of uncertainty in the relative effects, with overlapping credible intervals.

A recently published NMA was identified and subsequently excluded from this review for the following reasons. Firstly, it did not have a threshold for the proportion of ACS in the included study populations. The committee had agreed a threshold of >60% ACS (with 50-60% being acceptable but downgraded). One of the studies included in the published NMA had been excluded from this evidence review as the population of ACS was only 28%. In addition, a recent additional study was included in our evidence review but was not included in the published NMA. Lastly, the published NMA had grouped the drugs into their respective classes but the committee wanted to look at the specific drug combinations. A sensitivity analysis was conducted which showed that there was a difference in the direction of effect for the NMAs conducted for our evidence versus the recently published NMA. It was therefore agreed that using the recently published NMA would not be appropriate for decision-making for this evidence review.

The committee noted that the majority of evidence about combining antiplatelets and anticoagulants related to clopidogrel or aspirin rather than prasugrel or ticagrelor. The committee were concerned that bleeding risk may be higher in combinations of anticoagulants and prasugrel or ticagrelor and so given the lack of evidence were cautious about using them in this population. However, the studies using newer anticoagulants with clopidogrel and/or aspirin were reassuring in that outcomes were not inferior to those with warfarin, and previous guidance in favour of using combinations with warfarin were therefore judged inappropriate.

Cost effectiveness and resource use

No economic evaluations were identified for this review. It is noted that cost effectiveness analyses have been undertaken comparing oral anticoagulants in general populations where they are indicated such as AF and VTE and comparing antiplatelets in a general ACS population (see Evidence review A) and they are all options in current NHS practice for their respective indications. Many people who come into hospital with an ACS will already be on an oral anticoagulant that has been selected as most appropriate for them based on the evidence for that indication. However, it is not clear if risks and benefits from each respective treatment are the same in people that have both indications. In particular bleeding risk is a key clinical concern.

Unit costs were presented to aid committee consideration of cost-effectiveness. There is variation in the cost of anticoagulants and antiplatelets with newer agents being more expensive than older agents. Also, different combinations of these drugs will have different costs. Although the newer anticoagulants are more expensive, the committee estimated that over 50% of people will be taking these instead of warfarin. Also, while warfarin is the cheapest anticoagulant available, there are monitoring costs associated with warfarin as people taking warfarin need to have regular blood tests. The committee did not state which anticoagulant should be offered to people as there was insufficient clinical evidence to support using a specific combination over another. However the committee discussed that the majority of people that are already taking anticoagulants when they have an MI would usually continue taking the same anticoagulant post-MI. Clopidogrel and aspirin are lower cost than prasugrel and ticagrelor.

The recommendations are mostly unchanged from the previous guideline therefore they should not lead to significant change in practice or a substantial resource impact for the NHS in England.

1.8.2 Other factors the committee took into account

The need for regular monitoring of warfarin dosage was noted, with the attendant inconvenience for people taking this treatment and the additional cost. The possibility that warfarin control might be less tightly regulated in routine practice than in the clinical studies was also considered. Conversely, the committee noted that warfarin effects can be reversed if necessary and whilst reversal agents have recently become available for most of the other drugs these are more expensive.

It was noted that the available studies randomised subjects to treatment arms after PCI had been performed. There is therefore no evidence to inform choice of anticoagulant/antiplatelet combinations in the peri-procedural treatment phase.

The committee noted that there are different indications for anti-coagulation in people with ACS, and different patient risk factors (bleeding risk, thromboembolic risk and cardiovascular risk) and wishes. The evidence presented did not clearly favour any particular combination of anti-platelet and anticoagulant therapy and it was agreed that it is not possible to make specific recommendations for one treatment over another. Recommendations of a more general nature were formulated.

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Appendix A: Review protocols

Table 15: Review protocol: Combination therapy

ID	Field	Content
0.	PROSPERO registration number	CRD42019147574
1.	Review title	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an ACS and a separate indication for anticoagulation?
2.	Review question	What is the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an ACS and a separate indication for anticoagulation?
3.	Objective	To assess the most clinically and cost effective combination of antiplatelet and anticoagulant therapies in patients with an indication for long-term anticoagulant therapy, who have also

		had ACS.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE 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 the 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: • Adults (≥ 18 years) who have had ACS and a comorbid condition needing oral anticoagulation. The following groups may be included: • Patients with mechanical valve replacements • Patients with VTE needing continuing treatment • Patients who have left ventricular thrombus • Patients with atrial fibrillation (AF) who have had an MI and are taking anticoagulant agents • Mixed populations (ACS and stable) may be included if > 60% ACS

		Exclusion: None
7.	Intervention/Exposure/Test	Post discharge treatment (may be initiated in hospital but should not be stopped before discharge). • Dual antiplatelet therapy + warfarin • Dual antiplatelet therapy + rivaroxaban • Dual antiplatelet therapy + dabigatran • Dual antiplatelet therapy + apixaban • Dual antiplatelet therapy + Edoxaban • Aspirin + apixaban • Aspirin + warfarin • Aspirin + rivaroxaban • Aspirin + dabigatran • Aspirin + edoxaban • Clopidogrel/prasugrel/ticagrelor + warfarin • Clopidogrel/prasugrel/ticagrelor + rivaroxaban • Clopidogrel/prasugrel/ticagrelor + dabigatran • Clopidogrel/prasugrel/ticagrelor + apixaban • Clopidogrel/ prasugrel/ticagrelor + edoxaban Note Dual antiplatelet therapy = aspirin + clopidogrel/ticagrelor/prasugrel
8.	Comparator/Reference standard/Confounding factors	• Dual antiplatelet therapy alone • Warfarin alone • Rivaroxaban alone • Dabigatran alone • apixaban alone • Aspirin alone • Clopidogrel/prasugrel/ticagrelor alone • Edoxaban
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	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 - short term (≤30 days) • All-cause mortality- intermediate term (up to 1 year) • All-cause mortality- long term (>1 year) • Myocardial re-infarction - short term (≤30 days) • Myocardial re-infarction - intermediate term (up to 1 year) • Myocardial re-infarction - short term (≤30 days) • stroke - short term (≤30 days) • stroke - long term (>1 year) • stroke - short term (≤30 days) • Complications related to bleeding short term (≤30 days), intermediate term (up to 1 year), and long term (>1 year) including haemorrhagic stroke –(access bleeding and non-access bleeding need to be differentiated)- the following hierarchy of bleeding scales will be used: o BARC o Author's definition o TIMI o GUSTO Where possible, bleeding outcomes will be categorised into: o Major bleeding (including BARC 3-5 and as reported by author) o Minor bleeding (including BARC 2, TIMI and as reported by author). – 1 year • Health-related quality of life including EQ5D and SF-36.
13.	Secondary outcomes (important outcomes)	• Withdrawal of study drug due to any side effects • Probable and/or definite stent thrombosis at 1 year
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	• Indication for anticoagulant (mechanical heart values vs. VTE • Type of treatment of MI (PCI or CABG or medical) • Types of stents (bare metal stent vs. drug eluting stent)		
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	30/04/19		
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 [Senior Systematic Reviewers] • Miss Sophie Carlisle [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	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=147574
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, anti-coagulation
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

1

2 **Table 16: 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).[70] **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.[70]

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 17: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	01 January 2008 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	01 January 2008 – 22 July 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews 2008 to 2019 Issue 7 of 12 CENTRAL 2008 to 2019 Issue 7 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 or STE-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.	randomized controlled trial.pt.
39.	controlled clinical trial.pt.
40.	randomi#ed.ti,ab.
41.	placebo.ab.
42.	randomly.ti,ab.
43.	Clinical Trials as topic.sh.
44.	trial.ti.
45.	or/38-44
46.	Meta-Analysis/
47.	exp Meta-Analysis as Topic/

48.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
49.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
50.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
51.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
52.	(search* adj4 literature).ab.
53.	(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.
54.	cochrane.jw.
55.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
56.	or/46-55
57.	Percutaneous Coronary Intervention/
58.	Percutaneous coronary intervention*.ti,ab.
59.	(PPCI or PCI).ti,ab.
60.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
61.	PTCA.ti,ab.
62.	Angioplasty, Balloon, Coronary/
63.	exp Angioplasty/
64.	(Balloon adj3 coronary).ti,ab.
65.	((primary or coronary or transluminal or balloon) adj3 angioplasty).ti,ab.
66.	Coronary artery dilat*.ti,ab.
67.	exp *Stents/
68.	drug eluting stent*.ti,ab.
69.	(eluting adj3 stent*).ti,ab.
70.	((paclitaxel or sirolimus or everolimus or biolimus or ridaforolimus or zotarolimus or novolimus) adj3 stent*).ti,ab.
71.	or/57-70
72.	(37 or 71) and (45 or 56)
73.	Factor Xa Inhibitors/
74.	(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.
75.	rivaroxaban/
76.	DABIGATRAN/
77.	warfarin/
78.	oral anticoagul*.ti,ab.
79.	or/73-78
80.	72 and 79

1 **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 or STE-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.	random*.ti,ab.
37.	factorial*.ti,ab.
38.	(crossover* or cross over*).ti,ab.
39.	((doubl* or singl*) adj blind*).ti,ab.
40.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
41.	crossover procedure/
42.	single blind procedure/
43.	randomized controlled trial/
44.	double blind procedure/
45.	or/36-44
46.	systematic review/
47.	meta-analysis/
48.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
49.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
50.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.

51.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
52.	(search* adj4 literature).ab.
53.	(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.
54.	((pool* or combined) adj2 (data or trials or studies or results)).ab.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/46-56
58.	transluminal coronary angioplasty/ or percutaneous coronary intervention/
59.	Percutaneous coronary intervention*.ti,ab.
60.	(PPCI or PCI).ti,ab.
61.	Percutaneous Transluminal Coronary Angioplasty.ti,ab.
62.	PTCA.ti,ab.
63.	transluminal coronary angioplasty/ or percutaneous transluminal angioplasty/ or angioplasty/ or percutaneous transluminal angioplasty balloon/
64.	(Balloon adj3 coronary).ti,ab.
65.	((primary or coronary or transluminal or balloon) adj3 angioplasty).ti,ab.
66.	Coronary artery dilat*.ti,ab.
67.	or/58-66
68.	*stent/ or exp *cardiovascular stent/ or exp *drug eluting stent/ or exp *metal stent/
69.	drug eluting stent*.ti,ab.
70.	(eluting adj3 stent*).ti,ab.
71.	((paclitaxel or sirolimus or everolimus or biolimus or ridaforolimus or zotarolimus or novolimus) adj3 stent*).ti,ab.
72.	or/68-71
73.	35 or 67 or 72
74.	73 and (45 or 57)
75.	blood clotting factor 10a inhibitor/
76.	(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.
77.	apixaban/
78.	rivaroxaban/
79.	edoxaban/
80.	dabigatran/
81.	warfarin/
82.	oral anticoagul*.ti,ab.
83.	or/75-82
84.	74 and 83

1 **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 or STE-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.	MeSH descriptor: [Percutaneous Coronary Intervention] explode all trees
#24.	Percutaneous coronary intervention*:ti,ab
#25.	(PPCI or PCI):ti,ab
#26.	MeSH descriptor: [Angioplasty, Balloon, Coronary] explode all trees
#27.	Percutaneous Transluminal Coronary Angioplasty:ti,ab
#28.	PTCA:ti,ab
#29.	MeSH descriptor: [Angioplasty] explode all trees
#30.	(Balloon near/3 coronary):ti,ab
#31.	((primary or coronary or transluminal or balloon) near/3 angioplasty):ti,ab
#32.	Coronary artery dilat*:ti,ab
#33.	(or #23-#32)
#34.	MeSH descriptor: [Stents] explode all trees
#35.	(drug next eluting next stent*):ti,ab
#36.	(eluting near/3 stent*):ti,ab
#37.	((paclitaxel or sirolimus or everolimus or biolimus or ridaforolimus or zotarolimus or novolimus) near/3 stent*):ti,ab
#38.	(or #34-#37)
#39.	#22 or #33 or #38
#40.	MeSH descriptor: [Factor Xa Inhibitors] explode all trees
#41.	(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
#42.	MeSH descriptor: [Rivaroxaban] explode all trees
#43.	MeSH descriptor: [Dabigatran] explode all trees
#44.	MeSH descriptor: [Warfarin] explode all trees
#45.	oral anticoagul*:ti,ab
#46.	(or #40-#45)
#47.	#39 and #46

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 18: 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)

1 **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)

1 NHS EED and HTA (CRD) search terms

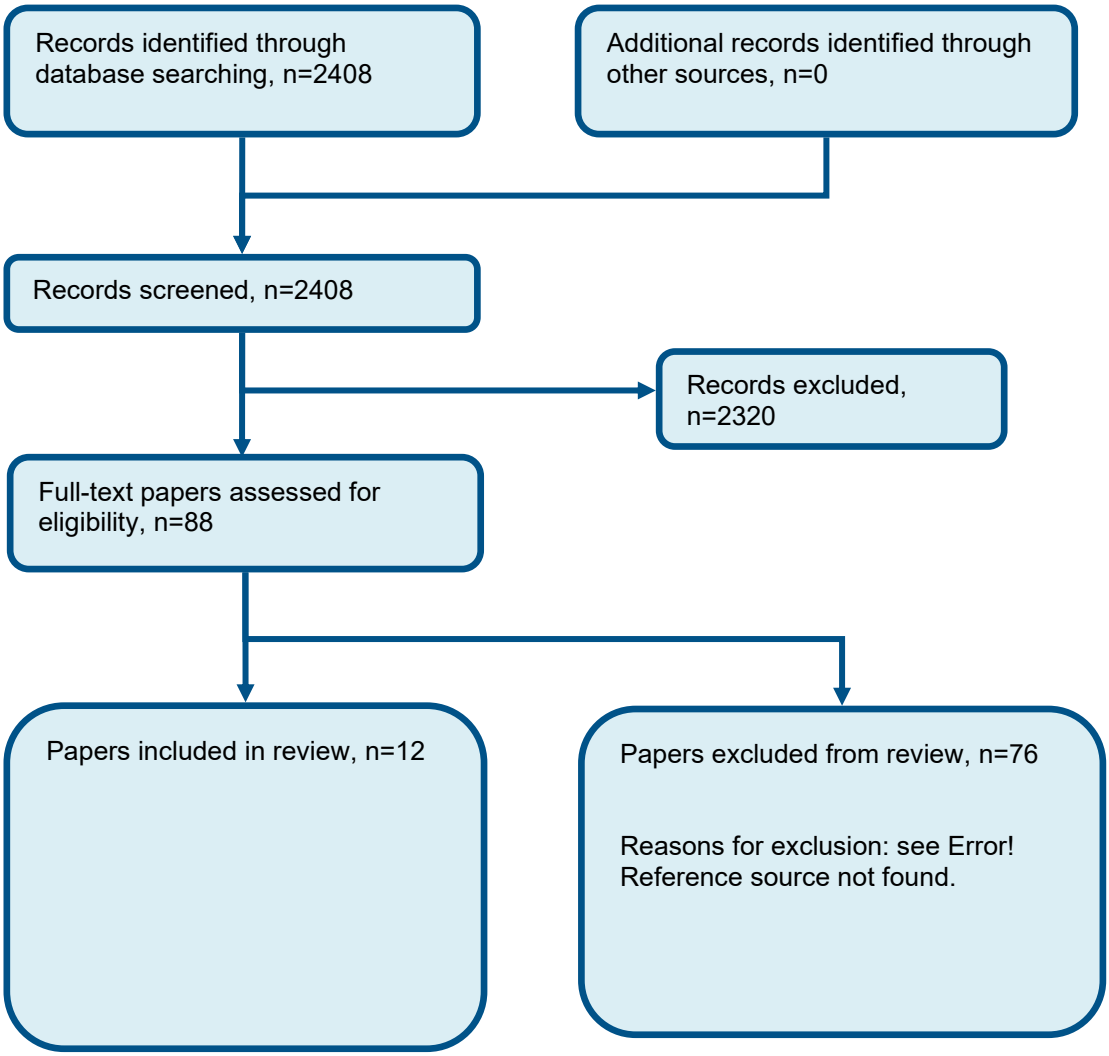
#1.	MeSH DESCRIPTOR Acute Coronary Syndrome
#2.	(MeSH DESCRIPTOR angina pectoris)
#3.	(MeSH DESCRIPTOR Angina, Unstable)
#4.	(MeSH DESCRIPTOR Coronary Thrombosis)
#5.	MeSH DESCRIPTOR Myocardial Infarction EXPLODE ALL TREES
#6.	#1 OR #2 OR #3 OR #4 OR #5
#7.	(MeSH DESCRIPTOR Heart Arrest)
#8.	((acute 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 1: Flow chart of clinical study selection for the review of combination therapy



Appendix D: Clinical evidence tables

Study (subsidiary papers)	AUGUSTUS trial: Lopes 2019[60] (Lopes 2018[62], Haller 2019[43])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=4614)
Countries and setting	Conducted in Multiple countries; Setting: Multicentre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with either active or a history of non-valvular atrial fibrillation or flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism. In addition, subjects must have had an acute coronary syndrome or percutaneous coronary intervention with a stent within the prior 14 days. Planned use of antiplatelet agents for at least 1 to 6 months. Males and Females ≥ 18 years of age. Women of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug
Exclusion criteria	Conditions other than atrial fibrillation that require chronic anticoagulation. (e.g. prosthetic mechanical heart valve); severe renal insufficiency (serum creatinine > 2.5 mg/dL or a calculated creatinine clearance < 30 mL/min; patients with a history of intracranial hemorrhage; patients have had or will undergo Coronary arterial bypass graft (CABG) for their index acute coronary syndrome (ACS) event; patients with known ongoing bleeding and patients with known coagulopathies; any contraindications or allergies to VKA, apixaban, or to intended P2Y12 antagonists or to aspirin
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): 70.7 (64.2-77.2). Gender (M:F): 1337/3277. Ethnicity: 92% White, 1.3% black, 3.1% asian, 0.4% Native American, 3.5% Other
Further population details	

Indirectness of population	No indirectness
Interventions	(n=1153) Intervention 1: Dual antiplatelet therapy + apixaban - aspirin + clopidogrel + apixaban. All participants received a P2Y inhibitor, left to the discretion of the treating physician, although 92% of participants had clopidogrel. Participants received apixiban (5 mg twice daily or to take 2.5 mg twice daily if they met two or more of the following dose-reduction criteria: were at least 80 years of age, had a weight of no more than 60 kg, or had a creatinine level of at least 1.5 mg per deciliter (133 µmol per liter) and aspirin (81 mg). After 6 months, patients were transitioned from their two trial interventions to receive antiplatelet and anticoagulant therapy according to the local standard of care. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves (Atrial fibrilation). 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (n=1154) Intervention 2: Dual antiplatelet therapy + warfarin - aspirin + clopidogrel + warfarin. All participants received a P2Y inhibitor, left to the discretion of the treating physician, although 92% of participants had clopidogrel. Participants received vitamin k antagnoist (dose adjusted to reach a target international normalized ratio (INR) within a range of 2.0 to 3.0) and aspirin (81 mg) (or placebo). After 6 months, patients were transitioned from their two trial interventions to receive antiplatelet and anticoagulant therapy according to the local standard of care. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (n=1153) Intervention 3: Clopidogrel + apixaban. Same as the apixaban + clopidogrel + aspirin group except participants received placebo instead of aspirin. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (n=1154) Intervention 4: Clopidogrel + warfarin. Same as the warfarin + clopidogrel + aspirin group except participants received placebo instead of aspirin. Duration 6 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear
Funding	Study funded by industry (Supported by Bristol-Myers Squibb and Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + APIXABAN versus ASPIRIN +

CLOPIDOGREL + WARFARIN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 38/1153, Group 2: 34/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 34/1153, Group 2: 34/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 8/1153, Group 2: 12/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 25/1145, Group 2: 29/1123
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 18
- Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 64/1145, Group 2: 80/1123
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 18; Group 2 Number missing: 21
- Actual outcome: Intracranial haemorrhage at 6 months; Group 1: 4/1145, Group 2: 4/1123
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 18; Group 2 Number missing: 21

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 6 months; Group 1: 11/1153, Group 2: 12/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing:

; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + APIXABAN versus CLOPIDOGREL + APIXABAN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 38/1153, Group 2: 39/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 34/1153, Group 2: 38/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 8/1153, Group 2: 5/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 25/1145, Group 2: 13/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 10
- Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 64/1145, Group 2: 32/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 10
- Actual outcome: Intracranial haemorrhage at 6 months; Group 1: 4/1145, Group 2: 1/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 10

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time

- Actual outcome: Stent thrombosis at 6 months; Group 1: 11/1153, Group 2: 21/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + APIXABAN versus CLOPIDOGREL + WARFARIN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 38/1153, Group 2: 40/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 34/1153, Group 2: 46/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 8/1153, Group 2: 14/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 25/1145, Group 2: 18/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 18
- Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 64/1145, Group 2: 51/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 8; Group 2 Number missing: 18
- Actual outcome: Intracranial haemorrhage at 6 months; Group 1: 4/1145, Group 2: 8/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing:

8; Group 2 Number missing: 18

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 6 months; Group 1: 11/1153, Group 2: 19/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + WARFARIN versus CLOPIDOGREL + APIXABAN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 34/1154, Group 2: 39/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 34/1154, Group 2: 38/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 12/1154, Group 2: 5/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 29/1123, Group 2: 13/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 21; Group 2 Number missing: 10
- Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 80/1123, Group 2: 32/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 21; Group 2 Number missing: 10

- Actual outcome: Intracranial haemorrhage at 6 months; Group 1: 4/1123, Group 2: 1/1143
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 21; Group 2 Number missing: 10

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 6 months; Group 1: 12/1154, Group 2: 21/1153
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + WARFARIN versus CLOPIDOGREL + WARFARIN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 34/1154, Group 2: 40/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 34/1154, Group 2: 46/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 12/1154, Group 2: 14/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 29/1123, Group 2: 18/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 18; Group 2 Number missing: 21
- Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 80/1123, Group 2: 51/1126

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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 18; Group 2 Number missing: 21
- Actual outcome: Intracranial haemorrhage at 6 months; Group 1: 4/1123, Group 2: 8/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 18; Group 2 Number missing: 21

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 6 months; Group 1: 12/1154, Group 2: 19/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL + APIXABAN versus CLOPIDOGREL + WARFARIN

Protocol outcome 1: All-cause mortality at intermediate term (>30 days up to 1 year)
- Actual outcome: All-cause mortality at 6 months; Group 1: 39/1153, Group 2: 40/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at intermediate term (>30 days up to 1 year)
- Actual outcome: Myocardial infarction at 6 months; Group 1: 38/1153, Group 2: 46/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at intermediate term (>30 days up to 1 year)
- Actual outcome: Stroke at 6 months; Group 1: 5/1153, Group 2: 14/1154
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at intermediate term (>30 days up to 1 year)
- Actual outcome: TIMI major bleeding at 6 months; Group 1: 13/1143, Group 2: 18/1126
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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing:

10; Group 2 Number missing: 18 - Actual outcome: TIMI major and minor bleeding at 6 months; Group 1: 32/1143, Group 2: 51/1126 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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 10; Group 2 Number missing: 18 - Actual outcome: Intracranial heamorrhage at 6 months; Group 1: 1/1143, Group 2: 8/1126 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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: 10; Group 2 Number missing: 18 Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time - Actual outcome: Stent thrombosis at 6 months; Group 1: 21/1153, Group 2: 19/1154 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 ; Blinding details: Blinded to aspirin vs placebo but not to apixaban vs warfarin; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at short term (≤30 days) ; All cause mortality at long term (>1 year); Myocardial re-infarction at short term (≤30 days) ; Myocardial re-infarction at long term (>1 year); Stroke - any type at short term (≤30 days) ; Stroke - any type at long term (>1 year); Complications related to bleeding at short term (≤30 days) ; Complications related to bleeding at long term (>1 year); Quality of life at any time; Withdrawal of study drug due to any side effects at any time

Study	**ENTRUST-AF PCI trial: Vranckx 2019[88]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1506)
Countries and setting	Conducted in Belgium, Germany, Italy, Netherlands, Switzerland, Ukraine; Setting: Hospital
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 monts
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Eligible patients had atrial fibrillation requiring oral anticoagulation, were aged at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome
Exclusion criteria	Patients with non-valvular atrial fibrillation not secondary to a reversible disorder were included and patients with mechanical heart valves, moderate-to-severe mitral stenosis, end-stage renal disease, and other major comorbidities were excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (IQR): Edoxaban group: 69 (63–77); VKA group: 70 (64–77). Gender (M:F): 1120/386. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=751) Intervention 1: Clopidogrel + edoxaban - Clopidogrel+ edoxaban. Patients assigned to the edoxaban regimen received a dose of 60 mg once daily and by default clopidogrel 75 mg once daily for 12 months. At the investigator's discretion, either prasugrel (5 mg or 10 mg once daily) or ticagrelor (90 mg twice daily) could be used instead of clopidogrel. The periprocedural antiplatelet therapy was per routine practice. The edoxaban dose was reduced to 30 mg once daily for patients with any of the following characteristics at randomisation or during the study: moderate or severe renal impairment (calculated creatinine clearance 15–50 mL/min), bodyweight 60 kg or less, or concurrent use of specific potent P-glycoprotein inhibitors (cyclosporine, dronedarone, erythromycin, or ketoconazole). At the end of the trial, patients in the edoxaban group could transition to VKA by receiving both edoxaban 30 mg once daily (15 mg for patients qualifying for dose reduction) and a VKA until an international normalised ratio (INR) of 2·0 was reached. At that point, edoxaban was stopped and the VKA was continued at the discretion of the treating physician, aiming for an INR of 2·0–3·0. Duration 12 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Not stated / Unclear 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (n=755) Intervention 2: Dual antiplatelet therapy + warfarin - aspirin + clopidogrel + warfarin. Patients who were randomly assigned to the VKA regimen received a VKA in combination with clopidogrel 75 mg once daily (or at the discretion of the investigator, prasugrel 5 mg or 10 mg once daily or ticagrelor 90 mg twice daily) for 12 months and aspirin (100 mg once daily) for a minimum of 1 month and up to 12 months' duration at the discretion of the investigator. The dose of VKA was adjusted to achieve and maintain a therapeutic INR of 2·0–3·0. INR measurements were taken once every 2–3 days until the value reached the therapeutic range; thereafter, ad-hoc INR measurements were performed at the discretion of the investigator. The choice of P2Y12 inhibitor and duration of aspirin treatment was predeclared by the investigator before random group assignment as guided by the clinical presentation. The use of gastric protection drugs that

	do not interact with cytochrome P450 2C19 (such as pantoprazole) was strongly recommended. Duration 12 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Not stated / Unclear 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear
Funding	Study funded by industry (Daiichi Sankyo Pharma Development and Daiichi Sankyo Europe)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL+ EDOXABAN versus ASPIRIN + CLOPIDOGREL + WARFARIN Protocol outcome 1: Complications related to bleeding at intermediate term (>30 days up to 1 year) - Actual outcome: Major or CRNM bleeding (ISTH) at 1 year; Group 1: 128/751, Group 2: 152/755 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome: Major bleeding (ISTH) at 1 year; Group 1: 45/751, Group 2: 48/755 Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	All-cause mortality at short term (≤30 days) ; All-cause mortality at intermediate term (>30 days up to 1 year) ; All cause mortality at long term (>1 year); Myocardial re-infarction at short term (≤30 days) ; Myocardial re-infarction at intermediate term (>30 days up to 1 year) ; Myocardial re-infarction at long term (>1 year); Stroke - any type at short term (≤30 days) ; Stroke - any type at intermediate term (>30 days up to 1 year) ; Stroke - any type at long term (>1 year); Complications related to bleeding at short term (≤30 days) ; Complications related to bleeding at long term (>1 year); Quality of life at any time; Withdrawal of study drug due to any side effects at any time; Probable and/or definite stent thrombosis at 1 year at any time

Study (subsidiary papers)	PIONEER AF-PCI trial: Gibson 2016[36] (Kerneis 2019[50], Kerneis 2018[49], Gibson 2015[35], Gibson 2017[37], Chi 2018[23])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2124)
Countries and setting	Conducted in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Democratic Republic of the Congo, Denmark, France, Germany, Italy, Malaysia, Mexico, Netherlands, Poland, Romania, Russia, South Africa, South Korea, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, USA; Setting: Multicentre
Line of therapy	Unclear
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients must undergo performance of PCI plus: 1. The minimum source documentation requirements for inclusion and exclusion criteria that specify a need for “documented medical history” are as follows: - Electrocardiogram, Holter monitor, pacemaker/defibrillator, or any device that provides a rhythm strip documenting paroxysmal, persistent, or permanent nonvalvular AF within 1 y before screening. OR - Electrocardiogram, Holter monitor, pacemaker/defibrillator, or any device that provides a rhythm strip documenting paroxysmal, persistent, or permanent nonvalvular AF that was performed more than 1 y before screening if the subject has been receiving oral anticoagulation therapy (VKA or a novel oral anticoagulant) for the AF for 3 mo immediately before the index PCI. 2. Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, laboratory assessment) and documented in the source documents.
Exclusion criteria	Any condition that contraindicates anticoagulant therapy or would confer an unacceptable risk of bleeding, such as, but not limited to: 1. Active internal bleeding 2. Clinically significant bleeding 3. Bleeding at a noncompressible site

	4. Bleeding diathesis within 30 d before randomization 5. A platelet count b90,000/μL at screening or prerandomization 6. A history of intracranial hemorrhage 7. Clinically significant gastrointestinal bleeding within 12 mo before randomization 8. Contraindications to the use of VKAs, ASA, or P2Y12 platelet inhibitors (clopidogrel, prasugrel, or ticagrelor), per prescribing information.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Group 1: 70.4 (9.1); group 2: 70.0 (9.1); group 3 69.9 (8.7). Gender (M:F): Define. Ethnicity: 94% white, 0.5% Black, 4% Asian, 1.4% other or unknown
Further population details	
Indirectness of population	No indirectness
Interventions	(n=709) Intervention 1: Clopidogrel + rivaroxaban. rivaroxaban at a dose of 15 mg once daily (or a dose of 10 mg once daily if they had moderate renal impairment, indicated by a creatinine clearance of 30 to 50 ml per minute) plus background single antiplatelet therapy with clopidogrel at a dose of 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants). Duration 12 months. Concurrent medication/care: Although aspirin could be administered up to 24 hours before the first dose of the trial drugs, aspirin at all doses was to be withheld after randomization.. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves (nonvalvular atrial fibrillation). 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (Mixed). (n=709) Intervention 2: Dual antiplatelet therapy + rivaroxaban - aspirin + clopidogrel + rivaroxaban. rivaroxaban at a dose of 2.5 mg twice daily plus background DAPT with low-dose aspirin (75 to 100 mg per day) and clopidogrel at a dose of 75 mg once daily (or ticagrelor at a dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) for a prespecified duration of 1, 6, or 12 months. Participants who received the treatment for 1 or 6 months then received rivaroxaban at a dose of 15 mg once daily (or 10 mg once daily if they had moderate renal impairment) plus background single antiplatelet therapy with low-dose aspirin (75 to 100 mg per day) for the remainder of the 12-month treatment period.. Duration 12 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves (nonvalvular atrial fibrillation). 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (Mixed). (n=706) Intervention 3: Dual antiplatelet therapy + warfarin - aspirin + clopidogrel + warfarin. dose/quantity, brand name, extra details. Duration 12 months. Concurrent medication/care: the vitamin K antagonist warfarin once daily (with dose adjustment to achieve a target INR of 2.0 to 3.0) plus background DAPT with low-dose aspirin (75 to 100 mg per day) and clopidogrel at a dose of 75 mg once daily (or ticagrelor at a

	dose of 90 mg twice daily or prasugrel at a dose of 10 mg once daily in ≤15% of participants) for a prespecified duration of 1, 6, or 12 months. Participants who received the treatment for 1 or 6 months then received warfarin once daily (with dose adjustment to achieve a target INR of 2.0 to 3.0) plus background single antiplatelet therapy with low-dose aspirin (75 to 100 mg per day) for the remainder of the 12-month treatment period.. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Mechanical valves 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear
Funding	Study funded by industry (Janssen Scientific Affairs and Bayer Pharmaceuticals)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL + RIVAROXABAN versus ASPIRIN + CLOPIDOGREL + RIVAROXABAN

Protocol outcome 1: All cause mortality at long term (>1 year)
- Actual outcome: Death from cardiovascular causes at 12 months; Group 1: 15/694, Group 2: 14/704
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: 15; Group 2 Number missing: 5
- Actual outcome: All-cause death at 12 months; Group 1: 16/696, Group 2: 17/706
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 3

Protocol outcome 2: Myocardial re-infarction at long term (>1 year)
- Actual outcome: Myocardial infarction at 12 months; Group 1: 19/694, Group 2: 17/704
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: 15; Group 2 Number missing: 5

Protocol outcome 3: Stroke - any type at long term (>1 year)
- Actual outcome: Stroke at 12 months; Group 1: 8/694, Group 2: 10/704
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: 15; Group 2 Number missing: 5

Protocol outcome 4: Complications related to bleeding at long term (>1 year)
- Actual outcome: Major bleeding at 12 months; Group 1: 14/696, Group 2: 12/706
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: 13; Group 2 Number missing: 3
- Actual outcome: Minor bleeding at 12 months; Group 1: 7/696, Group 2: 7/706
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: 13; Group 2 Number missing: 3

- Actual outcome: Bleeding requiring medical attention at 12 months; Group 1: 93/696, Group 2: 102/706
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: 13; Group 2 Number missing: 3

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 12 months; Group 1: 5/694, Group 2: 6/704
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: 15; Group 2 Number missing: 5

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL + RIVAROXABAN versus ASPIRIN + CLOPIDOGREL + WARFARIN

Protocol outcome 1: All cause mortality at long term (>1 year)
- Actual outcome: Death from cardiovascular diseases at 12 months; Group 1: 15/694, Group 2: 11/695
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: 15; Group 2 Number missing: 11
- Actual outcome: All-cause death at 12 months; Group 1: 16/696, Group 2: 13/697
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 13; Group 2 Number missing: 9

Protocol outcome 2: Myocardial re-infarction at long term (>1 year)
- Actual outcome: Myocardial infarction at 12 months; Group 1: 19/694, Group 2: 21/695
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: 15; Group 2 Number missing: 11

Protocol outcome 3: Stroke - any type at long term (>1 year)
- Actual outcome: Stroke at 12 months; Group 1: 8/694, Group 2: 7/695
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: 15; Group 2 Number missing: 11

Protocol outcome 4: Complications related to bleeding at long term (>1 year)
- Actual outcome: Bleeding requiring medical attention at 12 months; Group 1: 93/696, Group 2: 139/697
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: 13; Group 2 Number missing: 9
- Actual outcome: Major bleeding at 12 months; Group 1: 14/696, Group 2: 20/697
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: 13; Group 2 Number missing: 9
- Actual outcome: Minor bleeding at 12 months; Group 1: 7/696, Group 2: 13/697

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: 13; Group 2 Number missing: 9

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Stent thrombosis at 12 months; Group 1: 5/694, Group 2: 4/695
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: 15; Group 2 Number missing: 11

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ASPIRIN + CLOPIDOGREL + WARFARIN versus ASPIRIN + CLOPIDOGREL + RIVAROXABAN

Protocol outcome 1: All cause mortality at long term (>1 year)
- Actual outcome: Death from cardiovascular causes at 12 months; Group 1: 11/706, Group 2: 14/709
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 5
- Actual outcome: All-cause death at 12 months; Group 1: 13/697, Group 2: 17/706
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 9; Group 2 Number missing: 3

Protocol outcome 2: Myocardial re-infarction at long term (>1 year)
- Actual outcome: Myocardial infarction at 12 months; Group 1: 21/706, Group 2: 17/709
Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 11

Protocol outcome 3: Stroke - any type at long term (>1 year)
- Actual outcome: Stroke at 12 months; Group 1: 7/706, Group 2: 10/709
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: 9; Group 2 Number missing: 5

Protocol outcome 4: Complications related to bleeding at long term (>1 year)
- Actual outcome: Major bleeding at 12 months; Group 1: 20/697, Group 2: 12/706
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: 9; Group 2 Number missing: 3
- Actual outcome: Minor bleeding at 12 months; Group 1: 13/706, Group 2: 7/709
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: 9; Group 2 Number missing: 3
- Actual outcome: Bleeding requiring medical attention at 12 months; Group 1: 139/697, Group 2: 102/706
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: 9; Group 2 Number missing: 3 Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time - Actual outcome: Stent thrombosis at 12 months; Group 1: 4/706, Group 2: 6/709 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: 9; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	All-cause mortality at short term (≤30 days) ; All-cause mortality at intermediate term (>30 days up to 1 year) ; Myocardial re-infarction at short term (≤30 days) ; Myocardial re-infarction at intermediate term (>30 days up to 1 year) ; Stroke - any type at short term (≤30 days) ; Stroke - any type at intermediate term (>30 days up to 1 year) ; Complications related to bleeding at short term (≤30 days) ; Complications related to bleeding at intermediate term (>30 days up to 1 year) ; Quality of life at any time; Withdrawal of study drug due to any side effects at any time

Study (subsidiary papers)	RE-DUAL trial: Cannon 2017[19] (Oldgren 2019[75], Cannon 2016[20])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2725)
Countries and setting	Conducted in Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong (China), Hungary, India, Irish Republic, Israel, Italy, Japan, Mexico, Multiple countries, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, USA; Setting: Multicentre
Line of therapy	Unclear
Duration of study	Intervention time: Mean follow up 14 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	• Age ≥18 yr • Patients with NVAF who have been receiving an OAC or who are treatment-naïve prior to PCI; AF not secondary to a reversible disorder unless long-term anticoagulation was planned • ACS or unstable angina successfully treated by PCI and stenting or stable CAD with ≥1 lesion eligible for PCI that was successfully treated by elective PCI and stenting
Exclusion criteria	• Mechanical or biological heart valve prosthesis • Cardiogenic shock during current hospitalization • Use of fibrinolytic agents within 24 hr of randomization that will put the patient at high risk of bleeding (in the opinion of the investigator) • Stroke within 1 month prior to screening • Major surgery within 1 month prior to screening • Organ transplant, or on the waiting list for organ transplant • History of intraocular, spinal, retroperitoneal, or traumatic intra-articular bleeding, unless the causative factor has been permanently resolved • GI hemorrhage within 1 month before screening, unless the causative factor has been permanently resolved • A major bleeding episode including life-threatening bleeding within 1 month before screening • Hemorrhagic disorder or bleeding diathesis • Anemia or thrombocytopenia

	• Severe renal impairment (eCrCl <30 ml/min) • Active liver disease (ALT, AST, AP >3× ULN or known active hepatitis A, B, or C) • Recent malignancy or radiation therapy (≤6 months), unless life expectancy is >36 months • Continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, or St John's wort • Continued treatment with NSAIDs • Known allergy to dabigatran or warfarin or excipients of a study drug • Patients who should not be treated with an OAC • Contraindication to clopidogrel, ticagrelor, or ASA • Premenopausal women who are pregnant, breast-feeding, not surgically sterile, or not practicing 2 acceptable methods of birth control • Participation in another trial with an investigational drug or device within the past 30 days • Patients unable or unwilling to comply with the protocol, or with life expectancy shorter than the duration of the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=1744) Intervention 1: Clopidogrel + dabigatran. dual therapy with dabigatran etexilate (110 or 150mg twice daily) plus either clopidogrel or ticagrelor. 981 patients had 110mg, and 763 had 150 mg. All the patients were to receive either clopidogrel (75 mg daily) or ticagrelor (90 mg twice daily) for at least 12 months after randomization; the choice of agent was at the discretion of the investigator.. Duration 6 months minimum. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Not stated / Unclear (Non valcular atrial fibrilation). 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (Mixed). (n=981) Intervention 2: Clopidogrel + dabigatran. triple therapy with warfarin plus aspirin (≤100 mg daily) and either clopidogrel or ticagrelor (triple-therapy group). In the triple-therapy group, aspirin was discontinued after 1 month in patients in whom a bare-metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted . Duration 6 months minimum. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Indication for anticoagulant : Not stated / Unclear (Non valvular atrial fibrilation). 2. type of treatment of MI: PCI 3. Types of stents : Not stated / Unclear (Mixed).
Funding	Principal author funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLOPIDOGREL + DABIGATRAN versus ASPIRIN + CLOPIDOGREL + WARFARIN

Protocol outcome 1: All cause mortality at long term (>1 year)
- Actual outcome: Death at Mean 14 months; Group 1: 85/1744, Group 2: 48/981
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: ; Group 2 Number missing:

Protocol outcome 2: Myocardial re-infarction at long term (>1 year)
- Actual outcome: Myocardial infarction at Mean 14 months; Group 1: 70/1744, Group 2: 29/981
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: ; Group 2 Number missing:

Protocol outcome 3: Stroke - any type at long term (>1 year)
- Actual outcome: Stroke at Mean 14 months; Group 1: 26/1744, Group 2: 13/981
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: ; Group 2 Number missing:

Protocol outcome 4: Complications related to bleeding at long term (>1 year)
- Actual outcome: TIMI major bleeding at Mean 14 months; Group 1: 30/1744, Group 2: 37/981
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: ; Group 2 Number missing:
- Actual outcome: TIMI major or minor bleeding at Mean 14 months; Group 1: 56/1744, Group 2: 69/981
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: ; Group 2 Number missing:
- Actual outcome: Intracranial hemorrhage at Mean 14 months; Group 1: 4/1744, Group 2: 10/981
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: ; Group 2 Number missing:

Protocol outcome 5: Probable and/or definite stent thrombosis at 1 year at any time
- Actual outcome: Definite stent thrombosis at Mean 14 months; Group 1: 22/1744, Group 2: 8/981
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: ; Group 2 Number missing:

Protocol outcomes not reported by the study	All-cause mortality at short term (≤30 days) ; All-cause mortality at intermediate term (>30 days up to 1 year) ; Myocardial re-infarction at short term (≤30 days) ; Myocardial re-infarction at intermediate term (>30 days up to 1 year) ; Stroke - any type at short term (≤30 days) ; Stroke - any type at intermediate term

(>30 days up to 1 year) ; Complications related to bleeding at intermediate term (>30 days up to 1 year) ; Quality of life at any time; Withdrawal of study drug due to any side effects at any time	(≤30 days) ; Complications related to bleeding at short term

Appendix E: Forest plots

E.1 Warfarin + clopidogrel + aspirin versus warfarin + clopidogrel

E.2 AUGUSTUS data only

Figure 2: All-cause mortality (6 months)

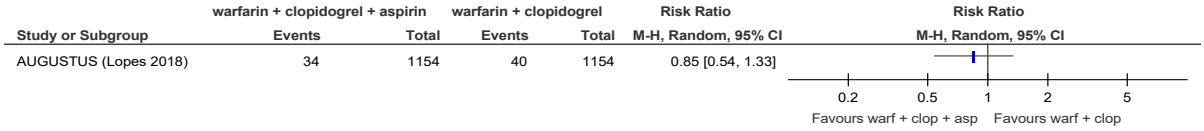


Figure 3: Myocardial infarction (6 months)

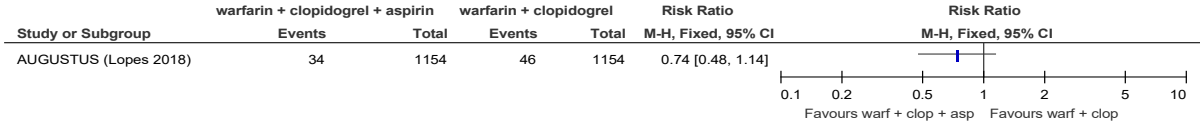


Figure 4: Stroke (6 months)

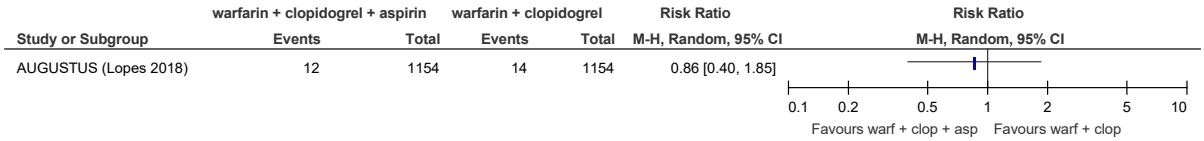


Figure 5: Any stent thrombosis (6 months)

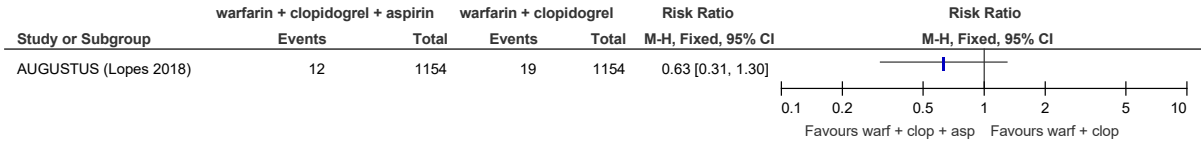
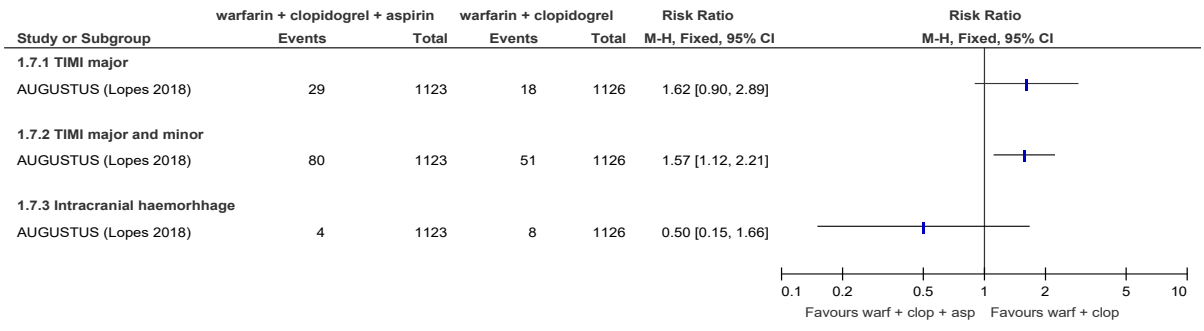


Figure 6: Complications relating to bleeding (6 months)



E.3 Warfarin + clopidogrel + aspirin versus dabigatran + clopidogrel

Figure 7: All-cause mortality (14 months)

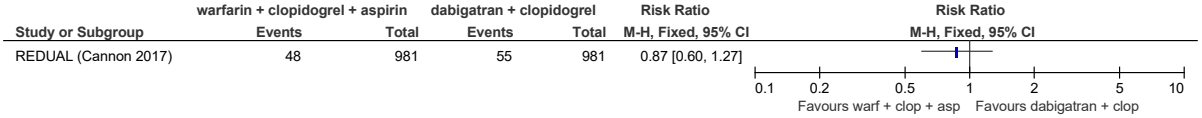


Figure 8: Myocardial infarction (14 months)

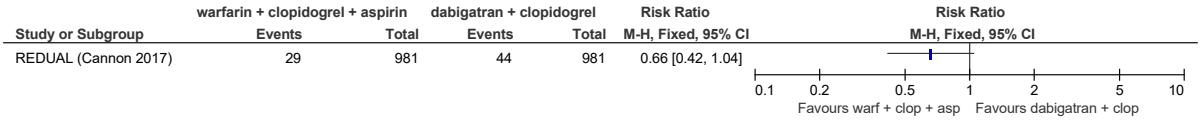


Figure 9: Stroke (14 months)

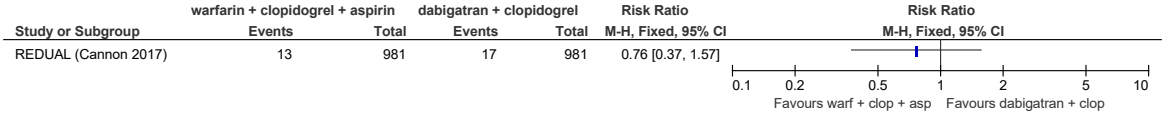


Figure 10: Definite stent thrombosis (14 months)

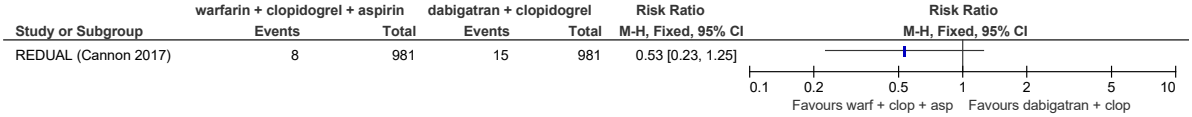
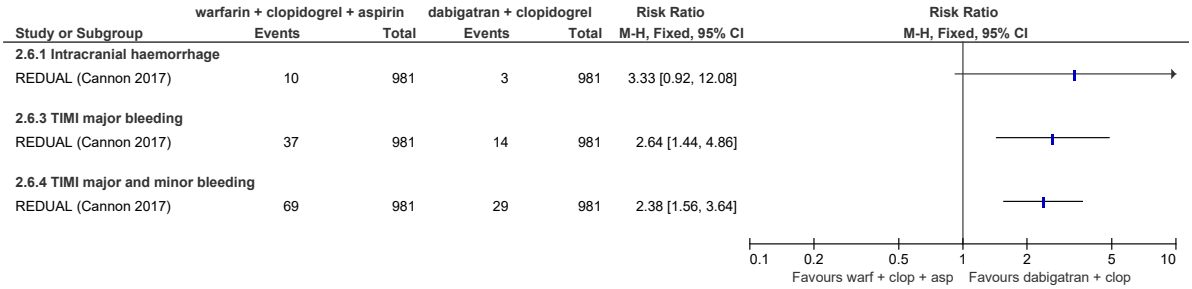


Figure 11: Complications relating to bleeding (14 months)



E.4 Rivaroxaban + clopidogrel + aspirin versus rivaroxaban + clopidogrel

Figure 12: All cause mortality (12 months)

Study or Subgroup	rivaroxaban + clopidogrel + aspirin Events	Total	rivaroxaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
PIONEER AF-PCI (Gibson 2016)	17	704	16	694	1.05 [0.53, 2.06]

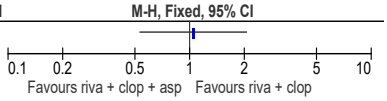


Figure 13: Myocardial infarction (12 months)

Study or Subgroup	rivaroxaban + clopidogrel + aspirin Events	Total	rivaroxaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
PIONEER AF-PCI (Gibson 2016)	17	704	19	694	0.88 [0.46, 1.68]

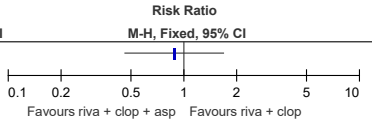


Figure 14: Stroke (12 months)

Study or Subgroup	rivaroxaban + clopidogrel + aspirin Events	Total	rivaroxaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
PIONEER AF-PCI (Gibson 2016)	10	704	8	694	1.23 [0.49, 3.10]

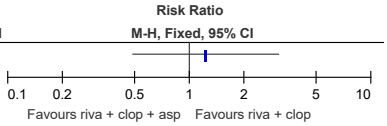


Figure 15: Stent thrombosis (12 months)

Study or Subgroup	rivaroxaban + clopidogrel + aspirin Events	Total	rivaroxaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
PIONEER AF-PCI (Gibson 2016)	6	704	5	694	1.18 [0.36, 3.86]

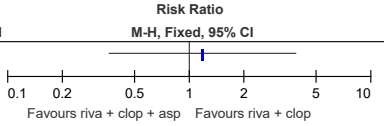
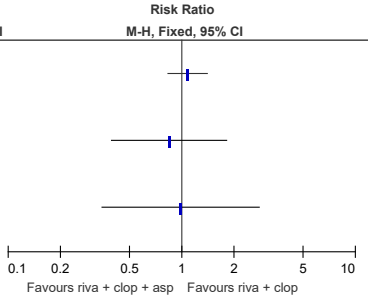


Figure 16: Complications relating to bleeding (12 months)

Study or Subgroup	rivaroxaban + clopidogrel + aspirin Events	Total	rivaroxaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
3.6.1 Bleeding requiring medical attention					
PIONEER AF-PCI (Gibson 2016)	102	706	93	696	1.08 [0.83, 1.40]
3.6.3 Major bleeding					
PIONEER AF-PCI (Gibson 2016)	12	706	14	696	0.85 [0.39, 1.81]
3.6.4 Minor bleeding					
PIONEER AF-PCI (Gibson 2016)	7	706	7	696	0.99 [0.35, 2.80]



E.5 Rivaroxaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Figure 17: All-cause mortality (12 months)

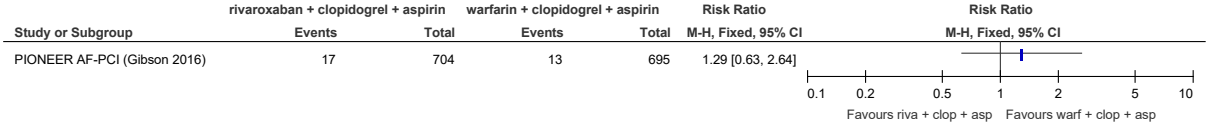


Figure 18: Myocardial infarction (12 months)

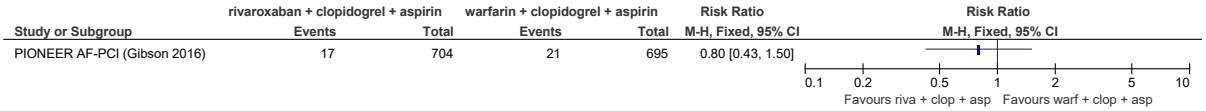


Figure 19: Stroke (12 months)

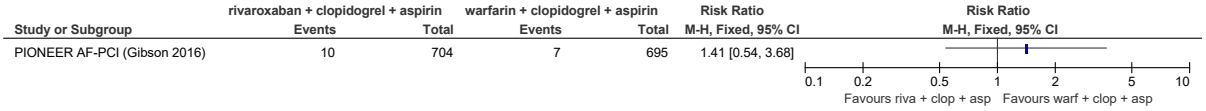


Figure 20: Stent thrombosis (12 months)

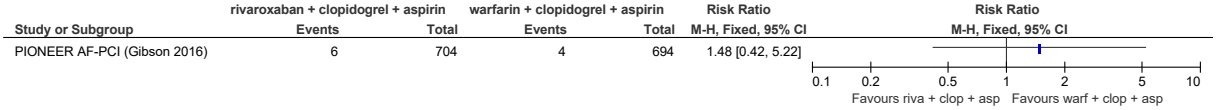
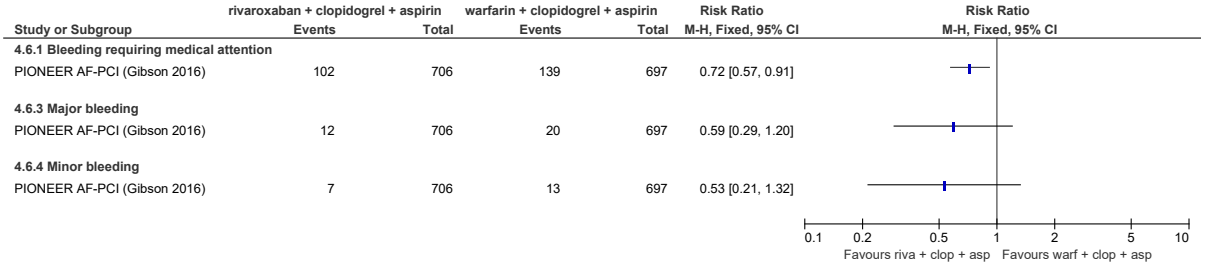


Figure 21: Complications relating to bleeding (12 months)



E.6 Warfarin + clopidogrel + aspirin versus rivaroxaban + clopidogrel

Figure 22: All-cause mortality **(12 months)**

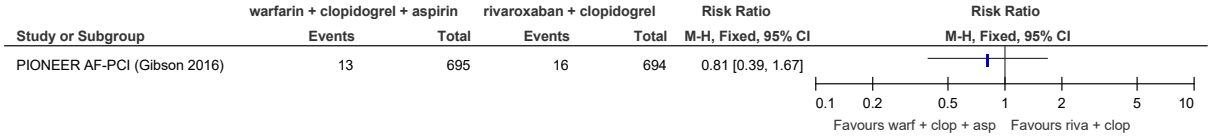


Figure 23: **Myocardial infarction (12 months)**

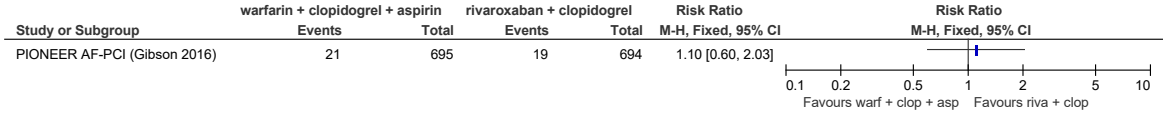


Figure 24: **Stroke (12 months)**

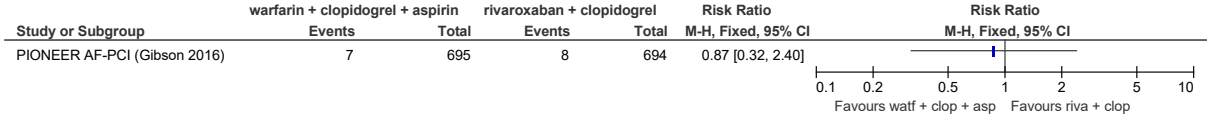


Figure 25: **Stent thrombosis (12 months)**

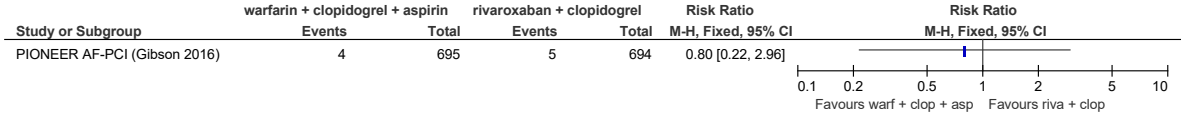
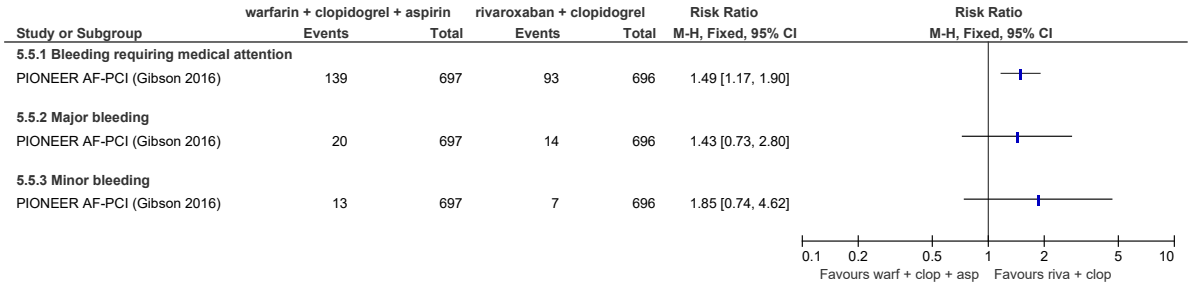


Figure 26: **Complications relating to bleeding (12 months)**



E.7 AUGUSTUS – Apixaban + clopidogrel + aspirin versus apixaban + clopidogrel

Figure 27: All-cause mortality (6 months)

Study or Subgroup	Apixaban + clop + asp Events	Total	Apixaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	38	1153	39	1153	0.97 [0.63, 1.51]

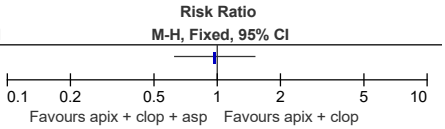


Figure 28: Myocardial infarction (6 months)

Study or Subgroup	Apixaban + clop + asp Events	Total	Apixaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	34	1153	38	1153	0.89 [0.57, 1.41]

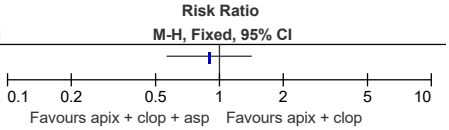


Figure 29: Stroke (6 months)

Study or Subgroup	Apixaban + clop + asp Events	Total	Apixaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	8	1153	5	1153	1.60 [0.52, 4.88]

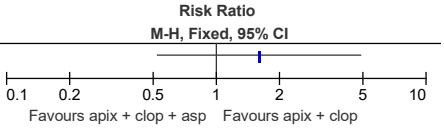


Figure 30: Any stent thrombosis (6 months)

Study or Subgroup	Apixaban + clop + asp Events	Total	Apixaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	11	1153	21	1153	0.52 [0.25, 1.08]

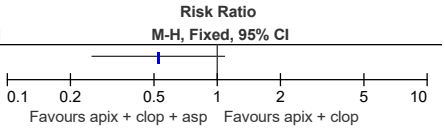
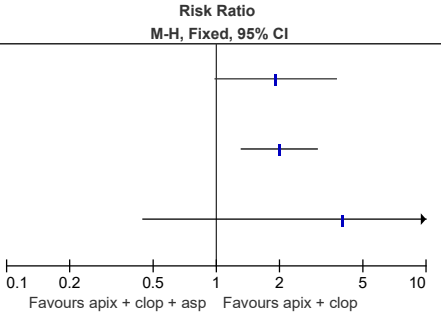


Figure 31: Complications related to bleeding (6 months)

Study or Subgroup	Apixaban + clop + asp Events	Total	Apixaban + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
6.5.1 TIMI major bleeding					
AUGUSTUS (Lopes 2018)	25	1145	13	1143	1.92 [0.99, 3.73]
6.5.2 TIMI major and minor bleeding					
AUGUSTUS (Lopes 2018)	64	1145	32	1143	2.00 [1.32, 3.03]
6.5.3 Intracranial haemorrhage					
AUGUSTUS (Lopes 2018)	4	1145	1	1143	3.99 [0.45, 35.67]



E.8 AUGUSTUS – Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Figure 32: All-cause mortality (6 months)

Study or Subgroup	Apix + clop + asp Events	Total	Warf + clop + asp Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	38	1153	34	1154	1.12 [0.71, 1.76]

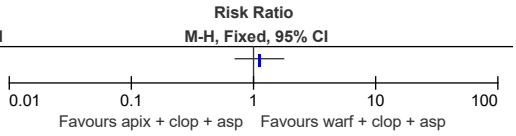


Figure 33: Myocardial infarction (6 months)

Study or Subgroup	Apix + clop + asp Events	Total	Warf + clop + asp Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	34	1153	34	1154	1.00 [0.63, 1.60]

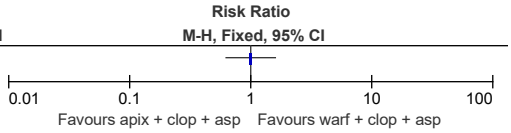


Figure 34: Stroke (6 months)

Study or Subgroup	Apix + clop + asp Events	Total	Warf + clop + asp Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	8	1153	12	1154	0.67 [0.27, 1.63]

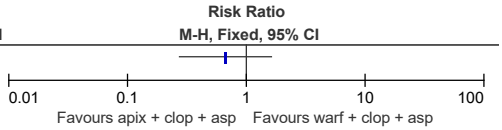


Figure 35: Any stent thrombosis (6 months)

Study or Subgroup	Apix + clop + asp Events	Total	Warf + clop + asp Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	11	1153	12	1154	0.92 [0.41, 2.07]

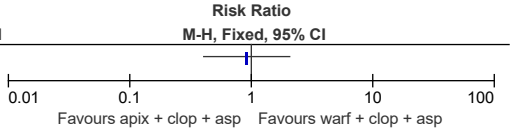
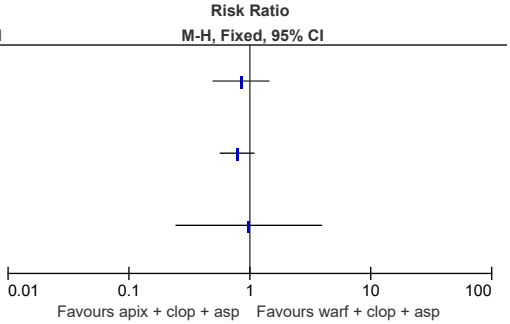


Figure 36: Complications related to bleeding (6 months)

Study or Subgroup	Apix + clop + asp Events	Total	Warf + clop + asp Events	Total	Risk Ratio M-H, Fixed, 95% CI
7.5.1 TIMI major bleeding					
AUGUSTUS (Lopes 2018)	25	1145	29	1123	0.85 [0.50, 1.43]
7.5.2 TIMI minor bleeding					
AUGUSTUS (Lopes 2018)	64	1145	80	1123	0.78 [0.57, 1.08]
7.5.3 Intracranial haemorrhage					
AUGUSTUS (Lopes 2018)	4	1145	4	1123	0.98 [0.25, 3.91]



E.9 AUGUSTUS – Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel

Figure 37: All-cause mortality (6 months)

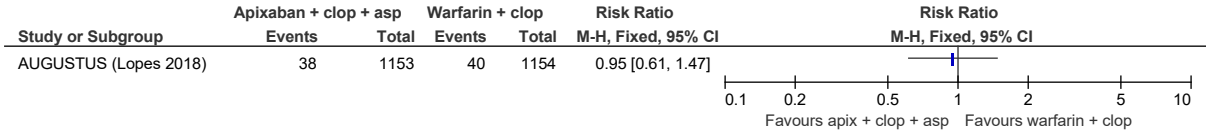


Figure 38: Myocardial infarction (6 months)

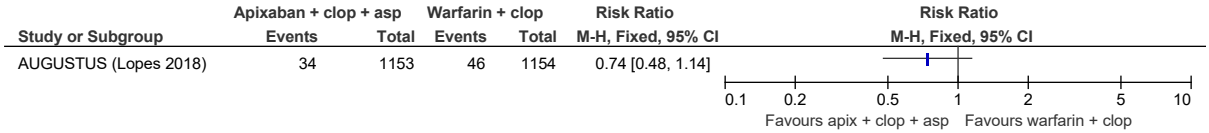


Figure 39: Stroke (6 months)

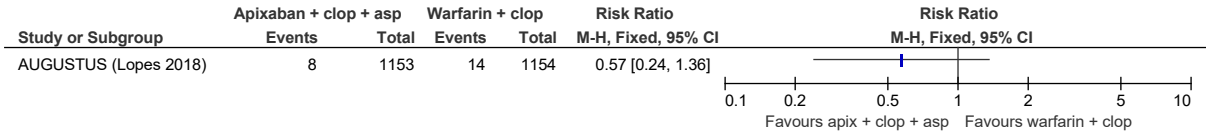


Figure 40: Any stent thrombosis (6 months)

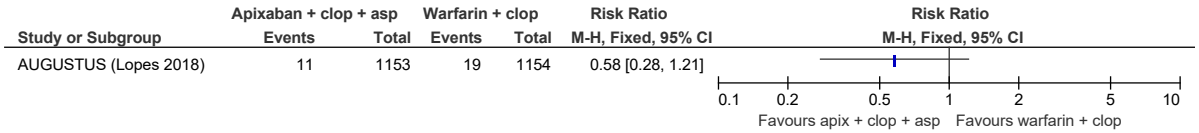
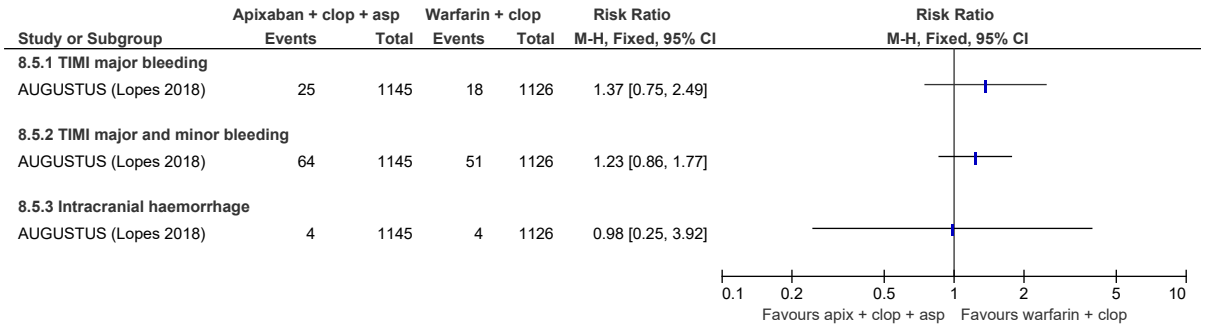


Figure 41: Complications related to bleeding (6 months)



E.10 AUGUSTUS – Warfarin + clopidogrel + aspirin versus apixaban + clopidogrel

Figure 42: All-cause mortality (6 months)

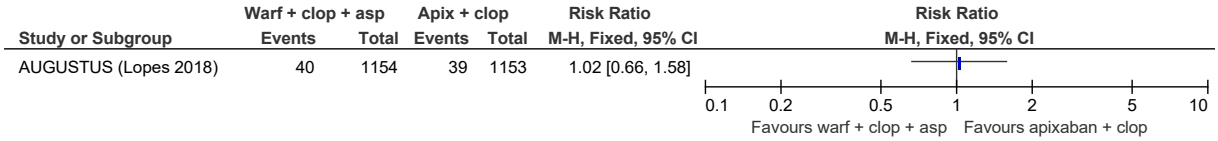


Figure 43: Myocardial infarction (6 months)

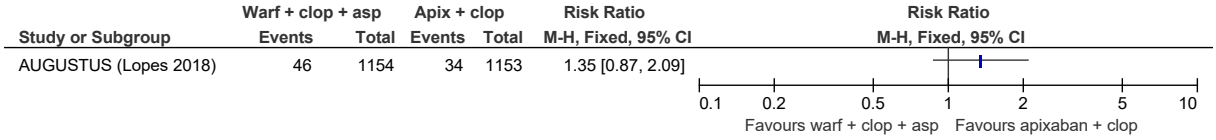


Figure 44: Stroke (6 months)

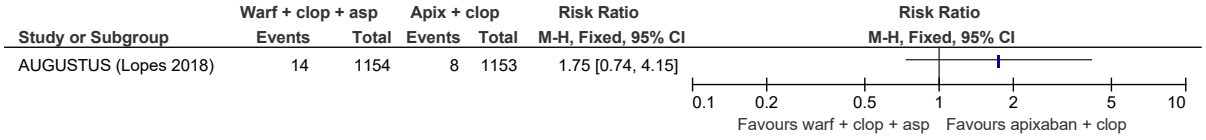


Figure 45: Any stent thrombosis (6 months)

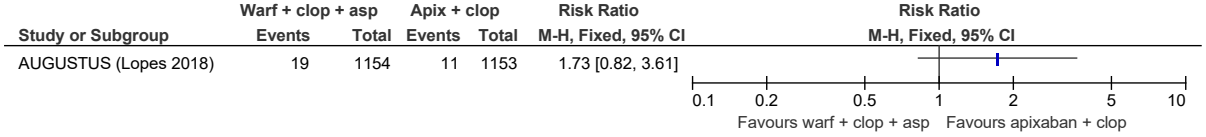
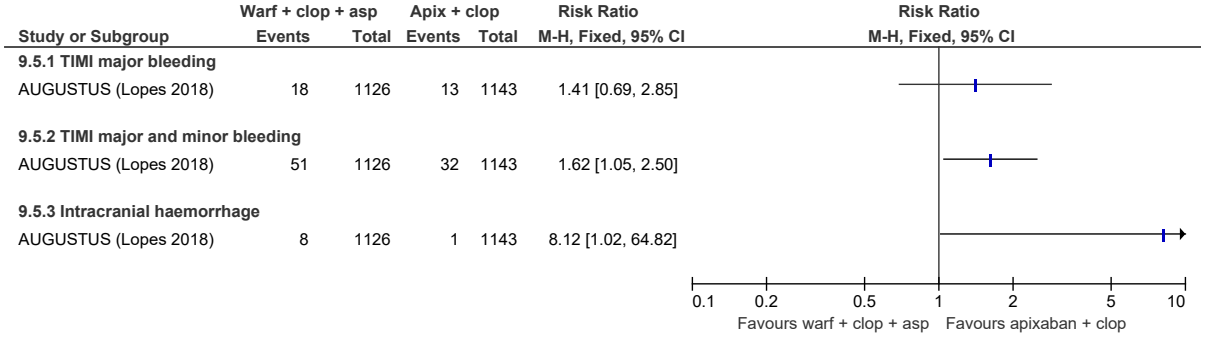


Figure 46: Complications relating to bleeding (6 months)



E.11 AUGUSTUS – Apixaban + clopidogrel versus warfarin + clopidogrel

Figure 47: All-cause mortality (6 months)

Study or Subgroup	Apixaban + clopidogrel Events	Total	Warfarin + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	39	1153	40	1154	0.98 [0.63, 1.51]

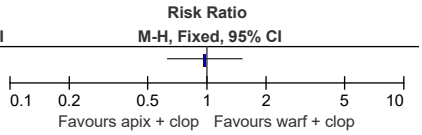


Figure 48: Myocardial infarction (6 months)

Study or Subgroup	Apixaban + clopidogrel Events	Total	Warfarin + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	38	1153	46	1154	0.83 [0.54, 1.26]

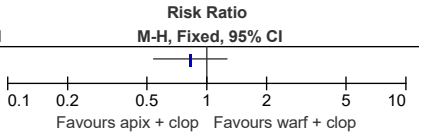


Figure 49: Stroke (6 months)

Study or Subgroup	Apixaban + clopidogrel Events	Total	Warfarin + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	5	1153	14	1154	0.36 [0.13, 0.99]

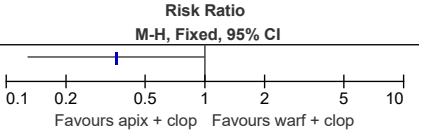


Figure 50: Any stent thrombosis (6 months)

Study or Subgroup	Apixaban + clopidogrel Events	Total	Warfarin + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
AUGUSTUS (Lopes 2018)	21	1153	19	1154	1.11 [0.60, 2.05]

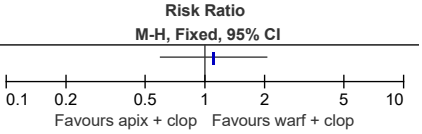
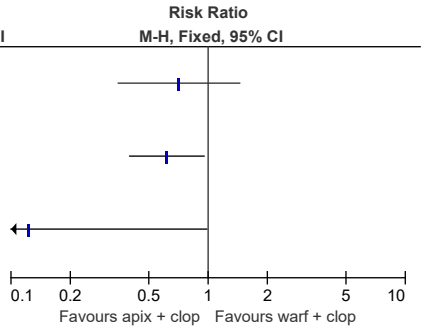


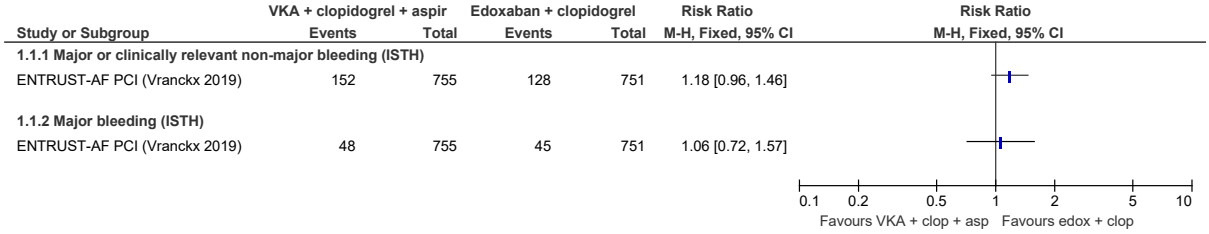
Figure 51: Complications related to bleeding (6 months)

Study or Subgroup	Apixaban + clopidogrel Events	Total	Warfarin + clopidogrel Events	Total	Risk Ratio M-H, Fixed, 95% CI
10.5.1 TIMI major bleeding					
AUGUSTUS (Lopes 2018)	13	1143	18	1126	0.71 [0.35, 1.45]
10.5.2 TIMI major and minor bleeding					
AUGUSTUS (Lopes 2018)	32	1143	51	1126	0.62 [0.40, 0.95]
10.5.3 Intracranial haemorrhage					
AUGUSTUS (Lopes 2018)	1	1143	8	1126	0.12 [0.02, 0.98]



E.12 VKA + clopidogrel + aspirin versus edoxaban + clopidogrel

Figure 52: Complications relating to bleeding (12 months)



E.13 Edoxaban + clopidogrel versus VKA + clopidogrel + aspirin

Figure 53: All-cause mortality (12 months)

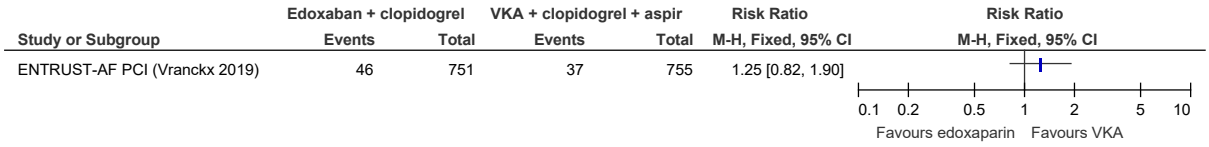


Figure 54: Stroke (12 months)

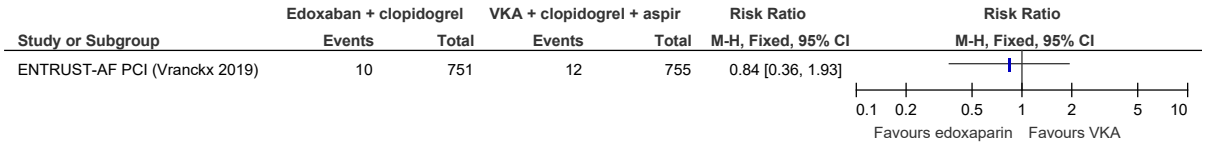


Figure 55: Myocardial infarction (12 months)

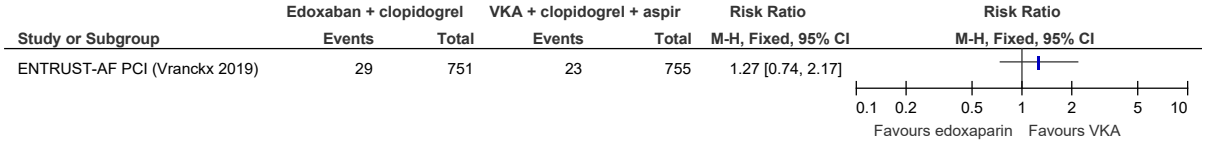


Figure 56: Stent thrombosis (12 months)

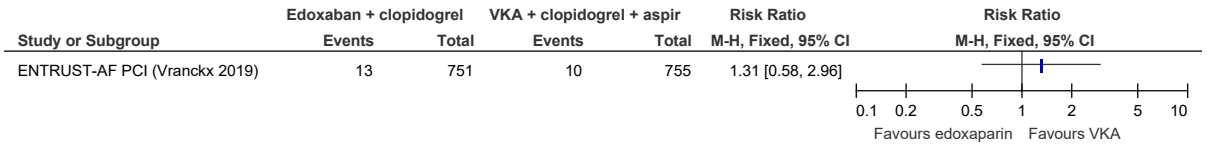
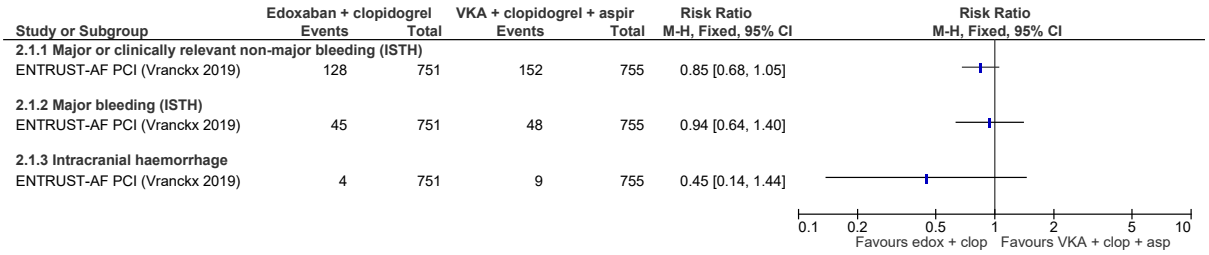


Figure 57: Complications relating to bleeding (12 months)



Appendix F: GRADE tables

Table 19: Clinical evidence profile: Warfarin + clopidogrel + aspirin versus warfarin + clopidogrel (AUGUSTUS data only)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Warfarin + clopidogrel + aspirin versus warfarin + clopidogrel	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	34/1154 (2.9%)	3.5%	RR 0.85 (0.54 to 1.33)	5 fewer per 1000 (from 16 fewer to 12 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/1154 (2.9%)	4%	RR 0.74 (0.48 to 1.14)	10 fewer per 1000 (from 21 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/1154 (1%)	1.2%	RR 0.86 (0.4 to 1.85)	2 fewer per 1000 (from 7 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Any stent thrombosis (follow-up 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	12/1154 (1%)	1.7%	RR 0.63 (0.31 to 1.3)	6 fewer per 1000 (from 12 fewer to 5 more)	⊕⊕OO LOW	IMPORTANT
Complications relating to bleeding - TIMI major (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	29/1123 (2.6%)	1.6%	RR 1.62 (0.9 to 2.89)	10 more per 1000 (from 2 fewer to 30 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications relating to bleeding - TIMI major and minor (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	80/1123 (7.1%)	4.5%	RR 1.57 (1.12 to 2.21)	26 more per 1000 (from 5 more to 54 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications relating to bleeding - Intracranial haemorhhage (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/1123 (0.36%)	0.7%	RR 0.5 (0.15 to 1.66)	3 fewer per 1000 (from 6 fewer to 5 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: Warfarin + clopidogrel + aspirin versus dabigatran + clopidogrel							No of patients		Effect		Quality	Importance
			Quality assessment									
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Warfarin + clopidogrel + aspirin**	**Dabigatran + clopidogrel**	**Relative (95% CI)**	**Absolute**		

All-cause mortality (follow-up 14 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	48/981 (4.9%)	5.6%	RR 0.87 (0.6 to 1.27)	7 fewer per 1000 (from 22 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (follow-up 14 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/981 (3%)	4.5%	RR 0.66 (0.42 to 1.04)	15 fewer per 1000 (from 26 fewer to 2 more)	⊕⊕OO LOW	CRITICAL
Stroke (follow-up 14 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/981 (1.3%)	1.7%	RR 0.76 (0.37 to 1.57)	4 fewer per 1000 (from 11 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Definite stent thrombosis (follow-up 14 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/981 (0.82%)	1.5%	RR 0.53 (0.23 to 1.25)	7 fewer per 1000 (from 12 fewer to 4 more)	⊕OOO VERY LOW	IMPORTANT
Complications relating to bleeding - Intracranial haemorrhage (follow-up 14 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/981 (1%)	0.3%	RR 3.33 (0.92 to 12.08)	7 more per 1000 (from 0 fewer to 33 more)	⊕⊕OO LOW	CRITICAL
Complications relating to bleeding - TIMI major bleeding (follow-up 14 months)											
1	randomised	serious[1]	no serious	no serious	no serious	none	37/981	1.4%	RR 2.64	23 more per	⊕⊕⊕O	CRITICAL

	trials		inconsistency	indirectness	imprecision		(3.8%)		(1.44 to 4.86)	1000 (from 6 more to 54 more)	MODERATE	
Complications relating to bleeding - TIMI major and minor bleeding (follow-up 14 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	69/981 (7%)	3%	RR 2.38 (1.56 to 3.64)	41 more per 1000 (from 17 more to 79 more)	⊕⊕⊕O MODERATE	CRITICAL

[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 once for serious imprecision, and twice for very serious imprecision

Table 21: Clinical evidence profile: Rivaroxaban + clopidogrel + aspirin versus rivaroxaban + clopidogrel

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban + clopidogrel + aspirin versus rivaroxaban + clopidogrel**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/704 (2.4%)	2.3%	RR 1.05 (0.53 to 2.06)	1 more per 1000 (from 11 fewer to 24 more)	⊕OOO VERY LOW	CRITICAL

Myocardial infarction (follow-up 12 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/704 (2.4%)	2.7%	RR 0.88 (0.46 to 1.68)	3 fewer per 1000 (from 15 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Stroke (follow-up 12 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/704 (1.4%)	1.2%	RR 1.23 (0.49 to 3.1)	3 more per 1000 (from 6 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Stent thrombosis (follow-up 12 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/704 (0.85%)	0.7%	RR 1.18 (0.36 to 3.86)	1 more per 1000 (from 4 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Complications relating to bleeding - Bleeding requiring medical attention (follow-up 12 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102/706 (14.4%)	13.4%	RR 1.08 (0.83 to 1.4)	11 more per 1000 (from 23 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
Complications relating to bleeding - Major bleeding (follow-up 12 months)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/706 (1.7%)	2%	RR 0.85 (0.39 to 1.81)	3 fewer per 1000 (from 12 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL
Complications relating to bleeding - Minor bleeding (follow-up 12 months)											

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/706 (0.99%)	1%	RR 0.99 (0.35 to 2.8)	0 fewer per 1000 (from 7 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL

[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 once for serious imprecision, and twice for very serious imprecision

Table 22: Clinical evidence profile: Rivaroxaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivaroxaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/704 (2.4%)	1.9%	RR 1.29 (0.63 to 2.64)	5 more per 1000 (from 7 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/704 (2.4%)	3%	RR 0.8 (0.43 to 1.5)	6 fewer per 1000 (from 17 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Stroke (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/704 (1.4%)	1%	RR 1.41 (0.54 to	4 more per 1000 (from 5 fewer to 27	⊕OOO VERY	CRITICAL

									3.68)	more)	LOW	
Stent thrombosis (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/704 (0.85%)	0.6%	RR 1.48 (0.42 to 5.22)	3 more per 1000 (from 3 fewer to 25 more)	⊕OOO VERY LOW	IMPORTANT
Complications relating to bleeding - Bleeding requiring medical attention (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102/706 (14.4%)	19.9%	RR 0.72 (0.57 to 0.91)	56 fewer per 1000 (from 18 fewer to 86 fewer)	⊕⊕OO LOW	CRITICAL
Complications relating to bleeding - Major bleeding (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/706 (1.7%)	2.9%	RR 0.59 (0.29 to 1.2)	12 fewer per 1000 (from 21 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Complications relating to bleeding - Minor bleeding (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/706 (0.99%)	1.9%	RR 0.53 (0.21 to 1.32)	9 fewer per 1000 (from 15 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL

[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 once for serious imprecision, and twice for very serious imprecision

Table 23: Clinical evidence profile: Warfarin + clopidogrel + aspirin versus Rivaroxaban + clopidogrel

Quality assessment							No of patients	Effect		Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Warfarin + clopidogrel + aspirin versus Rivaroxaban + clopidogrel**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/695 (1.9%)	2.3%	RR 0.81 (0.39 to 1.67)	4 fewer per 1000 (from 14 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Myocardial infarction (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	21/695 (3%)	2.7%	RR 1.1 (0.6 to 2.03)	3 more per 1000 (from 11 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Stroke (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/695 (1%)	1.2%	RR 0.87 (0.32 to 2.4)	2 fewer per 1000 (from 8 fewer to 17 more)	⊕OOO VERY LOW	CRITICAL
Stent thrombosis (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/695 (0.58%)	0.7%	RR 0.8 (0.22 to 2.96)	1 fewer per 1000 (from 5 fewer to 14 more)	⊕OOO VERY LOW	IMPORTANT
Complications related to bleeding - Bleeding requiring medical attention (follow-up 12 months)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	139/697	13.4%	RR 1.49	66 more per 1000 (from 23 more to	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness			(19.9%)		(1.17 to 1.9)	121 more)	LOW	
Complications related to bleeding - Major bleeding (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/697 (2.9%)	2%	RR 1.43 (0.73 to 2.8)	9 more per 1000 (from 5 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Complications related to bleeding - Minor bleeding (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/697 (1.9%)	1%	RR 1.85 (0.74 to 4.62)	9 more per 1000 (from 3 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL

[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 once for serious imprecision and twice for very serious imprecision

Table 24: Clinical evidence profile: AUGUSTUS – apixaban + clopidogrel + aspirin versus apixaban + clopidogrel

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban + clopidogrel + aspirin versus apixaban + clopidogrel**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	38/1153 (3.3%)	3.4%	RR 0.97 (0.63 to 1.51)	1 fewer per 1000 (from 13 fewer to 17 more)	⊕⊕OO LOW	CRITICAL

Myocardial infarction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	34/1153 (2.9%)	3.3%	RR 0.89 (0.57 to 1.41)	4 fewer per 1000 (from 14 fewer to 14 more)	⊕⊕OO LOW	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/1153 (0.69%)	0.4%	RR 1.6 (0.52 to 4.88)	2 more per 1000 (from 2 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Stent thrombosis (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/1153 (0.95%)	1.8%	RR 0.52 (0.25 to 1.08)	9 fewer per 1000 (from 13 fewer to 1 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications relating to bleeding - TIMI major bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	25/1145 (2.2%)	1.1%	RR 1.92 (0.99 to 3.73)	10 more per 1000 (from 0 fewer to 30 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications relating to bleeding - TIMI major and minor bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	64/1145 (5.6%)	2.8%	RR 2 (1.32 to 3.03)	28 more per 1000 (from 9 more to 57 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Complications relating to bleeding - Intracranial haemorrhage (follow-up 6 months)												
1	randomised	no serious	no serious	no serious	very serious[1]	none	4/1145	0.1%	RR 3.99	3 more per 1000	⊕⊕OO	IMPORTANT

	trials	risk of bias	inconsistency	indirectness			(0.35%)		(0.45 to 35.67)	(from 1 fewer to 35 more)	LOW	

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 25: Clinical evidence profile: AUGUSTUS – Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel + aspirin**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	38/1153 (3.3%)	3%	RR 1.12 (0.71 to 1.76)	4 more per 1000 (from 9 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	34/1153 (2.9%)	3%	RR 1 (0.63 to 1.6)	0 fewer per 1000 (from 11 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/1153 (0.69%)	1%	RR 0.67 (0.27 to 1.63)	3 fewer per 1000 (from 7 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT

Any stent thrombosis (follow-up 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	11/1153 (0.95%)	1%	RR 0.92 (0.41 to 2.07)	1 fewer per 1000 (from 6 fewer to 11 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding - TIMI major bleeding (follow-up 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25/1145 (2.2%)	2.6%	RR 0.85 (0.5 to 1.43)	4 fewer per 1000 (from 13 fewer to 11 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding - TIMI minor bleeding (follow-up 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	64/1145 (5.6%)	7.1%	RR 0.78 (0.57 to 1.08)	16 fewer per 1000 (from 31 fewer to 6 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - Intracranial haemorrhage (follow-up 6 months)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/1145 (0.35%)	0.4%	RR 0.98 (0.25 to 3.91)	0 fewer per 1000 (from 3 fewer to 12 more)	⊕⊕OO 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

Table 26: Clinical evidence profile: AUGUSTUS – Apixaban + clopidogrel + aspirin versus warfarin + clopidogrel

Quality assessment							No of patients	Effect		Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apixaban + clopidogrel + aspiri n versus warfarin + clopidogrel	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	38/1153 (3.3%)	3.5%	RR 0.95 (0.61 to 1.47)	2 fewer per 1000 (from 14 fewer to 16 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	34/1153 (2.9%)	4%	RR 0.74 (0.48 to 1.14)	10 fewer per 1000 (from 21 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	8/1153 (0.69%)	1.2%	RR 0.57 (0.24 to 1.36)	5 fewer per 1000 (from 9 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Any stent thrombosis (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	11/1153 (0.95%)	1.7%	RR 0.58 (0.28 to 1.21)	7 fewer per 1000 (from 12 fewer to 4 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - TIMI major bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	25/1145 (2.2%)	1.6%	RR 1.37 (0.75 to 2.49)	6 more per 1000 (from 4 fewer to 24 more)	⊕⊕OO LOW	IMPORTANT

Complications related to bleeding - TIMI major and minor bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	64/1145 (5.6%)	4.5%	RR 1.23 (0.86 to 1.77)	10 more per 1000 (from 6 fewer to 35 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - Intracranial haemorrhage (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/1145 (0.35%)	0.4%	RR 0.98 (0.25 to 3.92)	0 fewer per 1000 (from 3 fewer to 12 more)	⊕⊕OO 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

Table 27: Clinical evidence profile: AUGUSTUS – Warfarin + clopidogrel + aspirin versus apixaban + clopidogrel

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Warfarin + clopidogrel + aspirin versus apixaban + clopidogrel**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	40/1154 (3.5%)	3.4%	RR 1.02 (0.66 to 1.58)	1 more per 1000 (from 12 fewer to 20 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (follow-up 6 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	46/1154 (4%)	3%	RR 1.35 (0.87 to 2.09)	11 more per 1000 (from 4 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	14/1154 (1.2%)	0.7%	RR 1.75 (0.74 to 4.15)	5 more per 1000 (from 2 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Any stent thrombosis (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/1154 (1.6%)	1%	RR 1.73 (0.82 to 3.61)	7 more per 1000 (from 2 fewer to 26 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - TIMI major bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	18/1126 (1.6%)	1.1%	RR 1.41 (0.69 to 2.85)	5 more per 1000 (from 3 fewer to 20 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding - TIMI major and minor bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	51/1126 (4.5%)	2.8%	RR 1.62 (1.05 to 2.5)	17 more per 1000 (from 1 more to 42 more)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - Intracranial haemorrhage (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	8/1126 (0.71%)	0.1%	RR 8.12 (1.02 to 64.82)	7 more per 1000 (from 0 more to 64 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 28: Clinical evidence profile: AUGUSTUS – Apixaban + clopidogrel versus warfarin + clopidogrel

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Apixaban + clopidogrel versus warfarin + clopidogrel	Control	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	39/1153 (3.4%)	3.5%	RR 0.98 (0.63 to 1.51)	1 fewer per 1000 (from 13 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Myocardial infarction (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	38/1153 (3.3%)	4%	RR 0.83 (0.54 to 1.26)	7 fewer per 1000 (from 18 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Stroke (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/1153 (0.43%)	1.2%	RR 0.36 (0.13 to 0.99)	8 fewer per 1000 (from 0 fewer to 10 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Any stent thrombosis (follow-up 6 months)												
1	randomised	no serious	no serious	no serious	very	none	21/1153	1.7%	RR 1.11	2 more per 1000 (from 7 fewer to 18	⊕⊕OO	IMPORTANT

	trials	risk of bias	inconsistency	indirectness	serious[1]		(1.8%)		(0.6 to 2.05)	more)	LOW	
Complications related to bleeding - TIMI major bleeding												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/1143 (1.1%)	1.6%	RR 0.71 (0.35 to 1.45)	5 fewer per 1000 (from 10 fewer to 7 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding - TIMI major and minor bleeding (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	32/1143 (2.8%)	4.5%	RR 0.62 (0.4 to 0.95)	17 fewer per 1000 (from 2 fewer to 27 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Complications related to bleeding - Intracranial haemorrhage (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/1143 (0.09%)	0.7%	RR 0.12 (0.02 to 0.98)	6 fewer per 1000 (from 0 fewer to 7 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 29: Clinical evidence profile: VKA + clopidogrel + aspirin versus edoxaban + clopidogrel (ENTRUST-AF PCI)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**VKA + clopidogrel + aspirin**	**Edoxaban + clopidogrel**	**Relative (95% CI)**	**Absolute**		
Complications related to bleeding – Major or clinically relevant non-major bleeding (ISTH) (follow-up 12 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	152/755 (20.1%)	17%	RR 1.18 (0.96 to 1.46)	31 more per 1000 (from 7 fewer to 78 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications related to bleeding - Major bleeding (ISTH)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	48/755 (6.4%)	6%	RR 1.06 (0.72 to 1.57)	4 more per 1000 (from 17 fewer to 34 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 30: Clinical evidence summary: edoxaban + clopidogrel versus VKA + clopidogrel + aspirin (ENTRUST-AF PCI)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Edoxaban + clopidogrel versus VKA + clopidogrel + aspirin**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	46/751 (6.1%)	4.9%	RR 1.25 (0.82 to 1.9)	12 more per 1000 (from 9 fewer to 44 more)	⊕⊕⊕O MODERATE	CRITICAL
Stroke (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/751 (1.3%)	1.6%	RR 0.84 (0.36 to 1.93)	3 fewer per 1000 (from 10 fewer to 15 more)	⊕⊕OO LOW	

Myocardial infarction (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	29/751 (3.9%)	3.1%	RR 1.27 (0.74 to 2.17)	8 more per 1000 (from 8 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Stent thrombosis (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	13/751 (1.7%)	1.3%	RR 1.31 (0.58 to 2.96)	4 more per 1000 (from 5 fewer to 25 more)	⊕⊕OO LOW	IMPORTANT
Complications related to bleeding - Major or clinically relevant non-major bleeding (ISTH) (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	128/751 (17%)	20.1%	RR 0.85 (0.68 to 1.05)	30 fewer per 1000 (from 64 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications related to bleeding - Major bleeding (ISTH) (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	45/751 (6%)	6.4%	RR 0.94 (0.64 to 1.4)	4 fewer per 1000 (from 23 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Complications related to bleeding - Intracranial haemorrhage (follow-up 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	4/751 (0.53%)	1.2%	RR 0.45 (0.14 to 1.44)	7 fewer per 1000 (from 10 fewer to 5 more)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Network meta-analysis: Sensitivity analyses using Lopes 2019

Introduction

Whilst reviewing the pairwise outcome data, the committee found it difficult to reach an over-arching conclusion about the most clinically effective treatment/s. The committee considered the proposal of conducting network meta-analyses (NMAs) in this evidence review to inform decision-making. Traditionally, an NMA can provide some clarity around the relative effects for treatments within a network and aid decision-making.

A recently published NMA was identified as being relevant for this review (Lopes 2019) [61]. Whilst reviewing this publication some differences between the evidence-base of Lopes 2019 and this guideline evidence-base were highlighted:

- The committee agreed a threshold of >60% ACS (with 50-60% being acceptable but downgraded) for inclusion in this review, Lopes 2019 did not have a threshold for ACS
- One of the studies (included in Lopes 2019) was excluded from this evidence review as the population of ACS was only 28% [27]
- A recent additional study was included this evidence review but was not included in the published NMA [88]
- This review has analysed drugs separately, Lopes 2019 has combined drugs into their classes in their analyses, e.g. apixaban and rivaroxaban are classified as NOACs

Objective

Sensitivity analyses were conducted to assess if it was appropriate to use Lopes 2019 to inform decision-making. The sensitivity analyses took into account the current guideline evidence-base for the question on the most clinically and cost effective combination of antiplatelet and anticoagulant therapies for people who have had an ACS and a separate indication for anticoagulation.

Statistical Methods

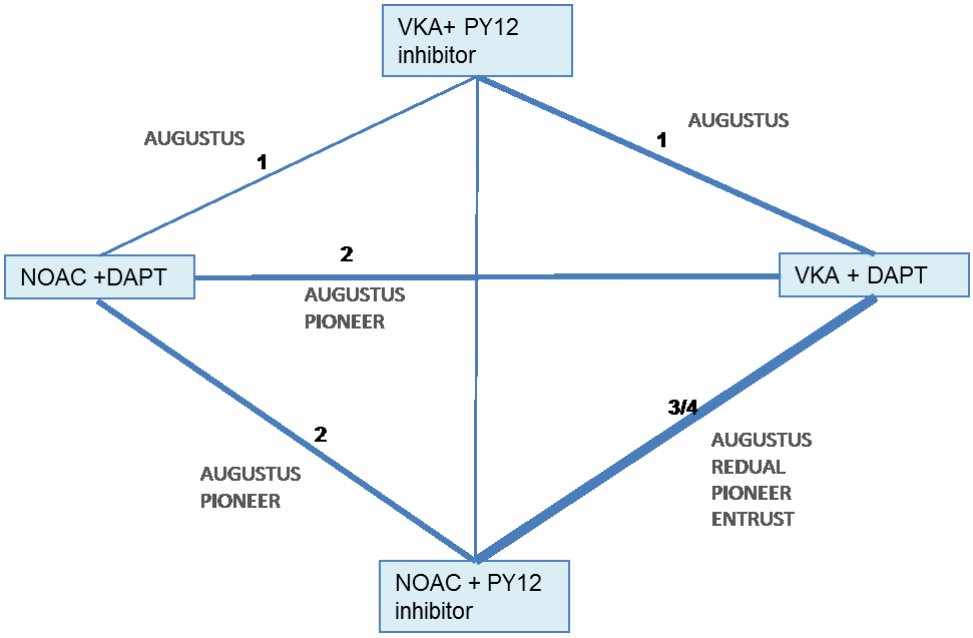
The description of the statistical methods used is described elsewhere in the guideline, see NMA document. Whilst relative risk values have been reported in this evidence review for pairwise meta-analyses, odd ratios have been used to be consistent with the summary statistics reported in Lopes 2019.

Results

Network meta-analyses were conducted for three outcomes (all-cause mortality, myocardial infarction and major bleeding). All of the networks were informed by outcome data from the four trials included in this evidence review. Outcome data for all-cause mortality, myocardial infarction and major bleeding can be found in **Table 31**, **Table 32**, **Table 33**, respectively. The network diagram for all of the outcomes is displayed in **Figure 58**.

The results (odd ratios) for the network meta-analyses were compared in plots for each of the outcomes, as seen in **Figure 59**, **Figure 60**, **Figure 61**. Checks for inconsistency were conducted following methods described in the NMA chapter. No inconsistency was identified in the three networks.

Figure 58: Network diagram for the three outcomes (all-cause mortality, myocardial infarction and major bleeding)



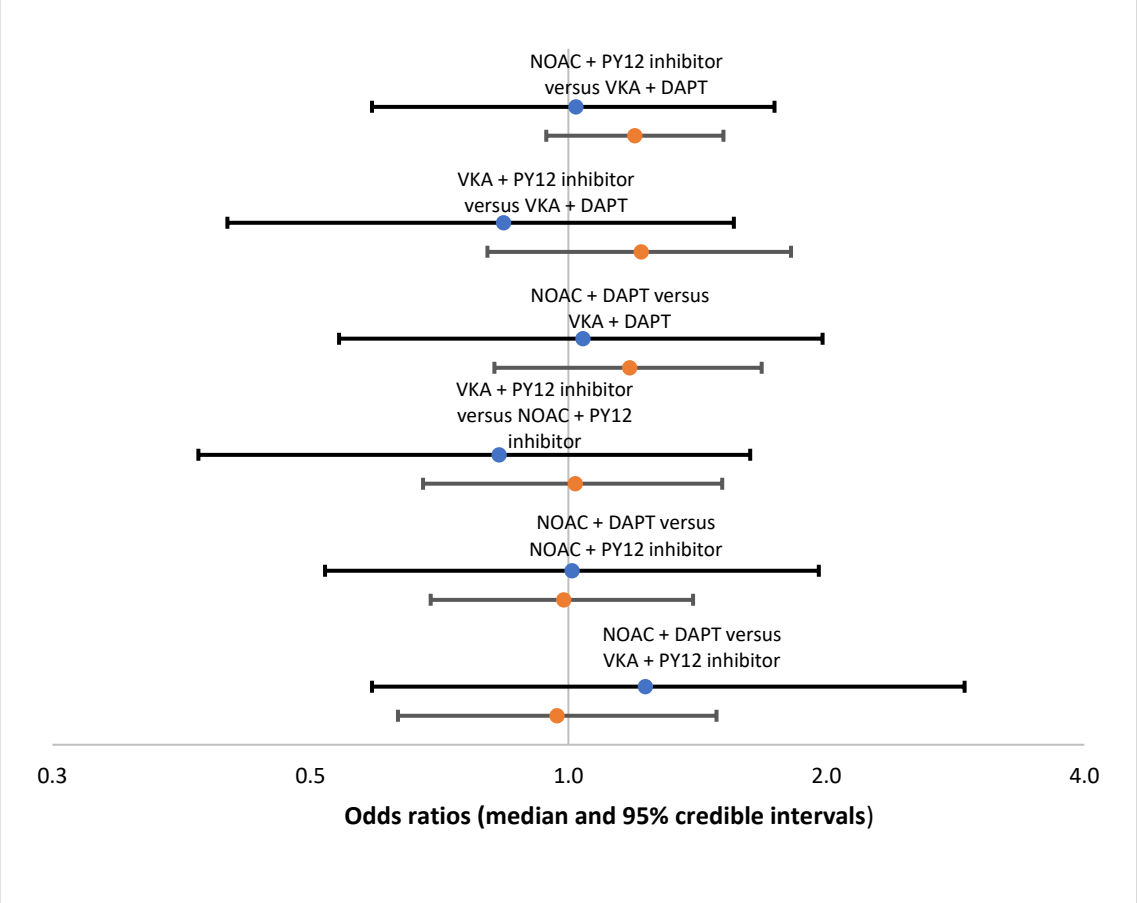
All-cause mortality

Table 31: Study data for all-cause mortality network meta-analysis – guideline review evidence-base

	Interventions				Number of events/number of participants (per intervention)			
Study ID	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
REDUAL	VKA + DAPT	NOAC + PY12 inhibitor			48/981	55/981		
PIONEER	NOAC + PY12 inhibitor	NOAC + DAPT	VKA + DAPT		16/694	17/704	13/695	
AUGUSTUS	VKA + DAPT	NOAC + DAPT	NOAC + PY12 inhibitor	VKA + PY12 inhibitor	34/1154	38/1153	39/1153	40/1154
ENTRUST	NOAC + PY12 inhibitor	VKA + DAPT			46/751	37/755		

VKA – vitamin K antagonist; DAPT – dual antiplatelet therapy; NOAC – novel oral antagonist

Figure 59: Sensitivity analysis results (odds ratios) – NMA conducted for this evidence review compared with Lopes 2019 results – all-cause mortality



Blue circle = Lopes 2019; Orange circle = National Guideline Centre

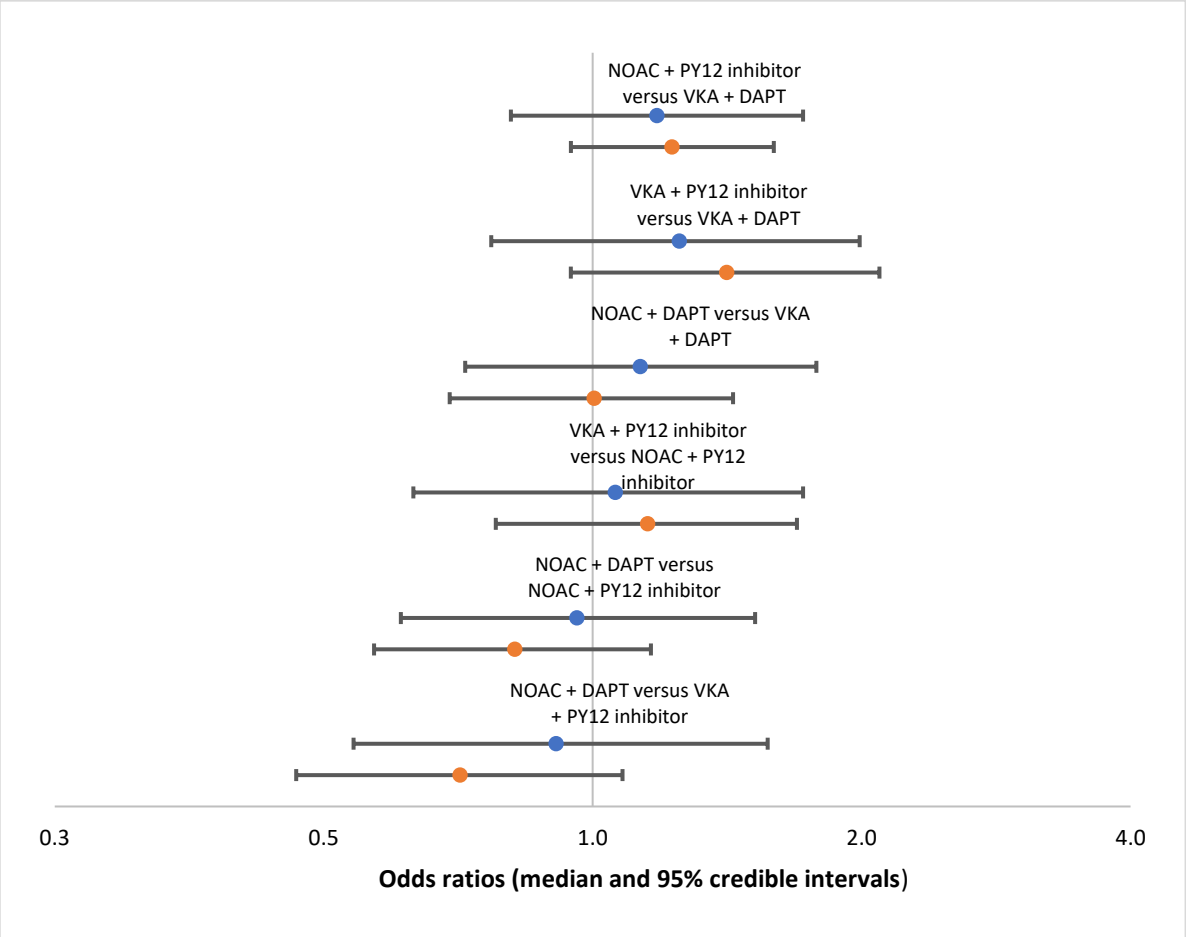
Myocardial infarction

Table 32: Study data for myocardial infarction network meta-analysis – guideline review evidence-base

	Intervention				Number of events/number of participants (per intervention)			
Study ID	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
REDUAL	VKA + DAPT	NOAC + PY12 inhibitor			29/981	44/981		
PIONEER	NOAC + PY12 inhibitor	NOAC + DAPT	VKA + DAPT		19/694	17/704	21/695	
AUGUSTUS	VKA + DAPT	NOAC + DAPT	NOAC + PY12 inhibitor	VKA + PY12 inhibitor	34/1154	34/1153	38/1153	46/1154
ENTRUST	NOAC + PY12 inhibitor	VKA + DAPT			29/751	23/755		

VKA – vitamin K antagonist; DAPT – dual antiplatelet therapy; NOAC – novel oral antagonist

Figure 60: Sensitivity analysis results (odds ratios) – NMA conducted for this evidence review compared with Lopes 2019 results – myocardial infarction



Blue circle = Lopes 2019; Orange circle = National Guideline Centre

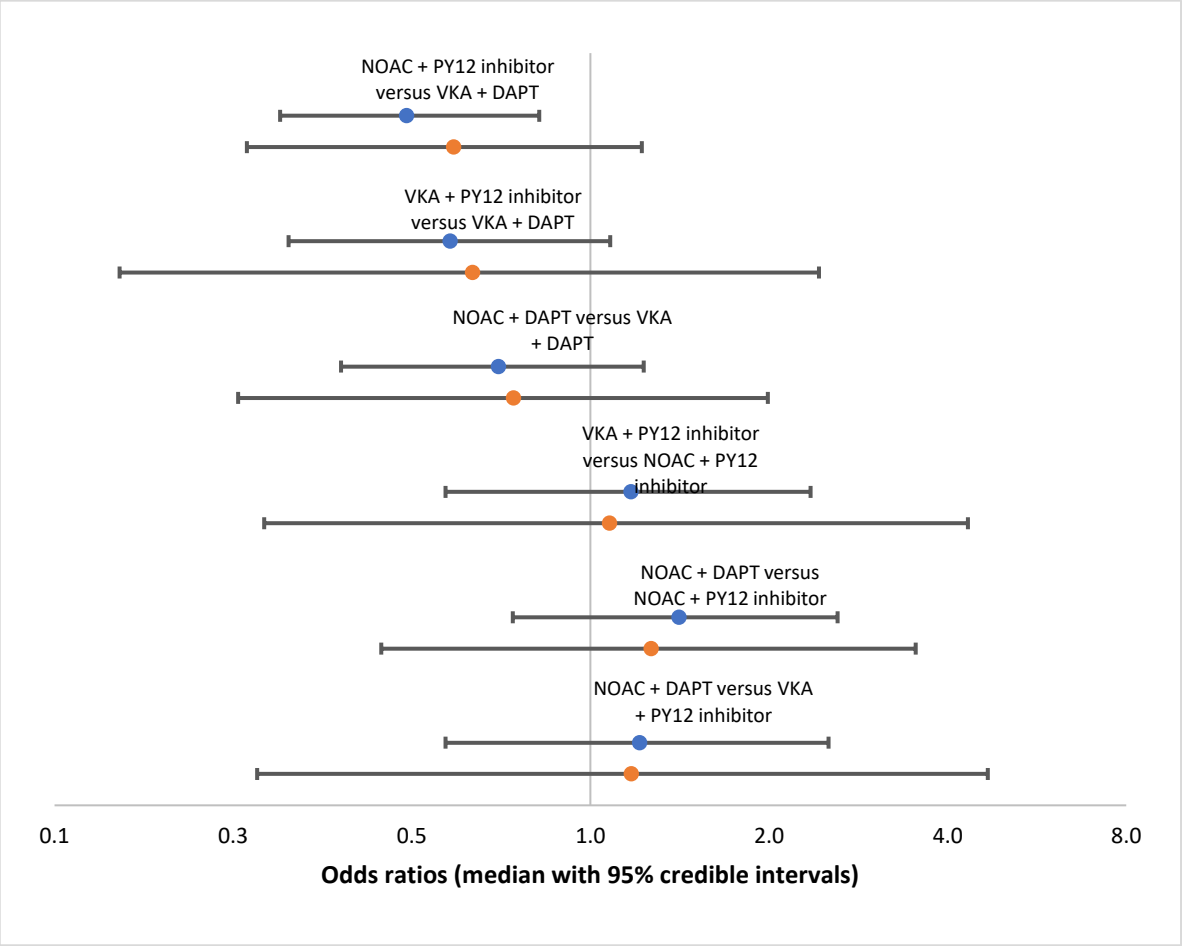
Major bleeding

Table 33: Study data for major bleeding network meta-analysis – guideline review evidence-base

	Interventions				Number of events/number of participants (per intervention)			
Study ID	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
REDUAL	VKA + DAPT	NOAC + PY12 inhibitor			37/981	14/981		
PIONEER	NOAC + PY12 inhibitor	NOAC + DAPT	VKA + DAPT		14/696	12/706	20/697	
AUGUSTUS	VKA + DAPT	NOAC + DAPT	NOAC + PY12 inhibitor	VKA + PY12 inhibitor	29/1123	25/1145	13/1143	18/1126
ENTRUST	NOAC + PY12 inhibitor	VKA + DAPT			45/751	48/755		

VKA – vitamin K antagonist; DAPT – dual antiplatelet therapy; NOAC – novel oral antagonist

Figure 61: Sensitivity analysis results (odds ratios) – NMA conducted for this evidence review compared with Lopes 2019 results – major bleeding



Blue circle = Lopes 2019; Orange circle = National Guideline Centre

Conclusion

The sensitivity analyses showed that there seemed to be good agreement between the results for major bleeding, but there are some differences in the point estimates for the other two outcomes. Since there were some differences in the direction of relative effectiveness estimated from the two evidence bases, the committee concluded that Lopes 2019 is not representative of the guideline's evidence base and its results did not influence decision-making. Nevertheless, based on the guideline-specific results for the three outcomes considered, there was not enough evidence to conclude any differences between the clinical effectiveness and harms of these treatments. There is a lot of uncertainty in the relative effects, with overlapping credible intervals. The committee concluded that there is not enough evidence to conclude these treatments are more effective or safer than the others.

See section 1.8 for full details on the committee's discussion of the evidence.

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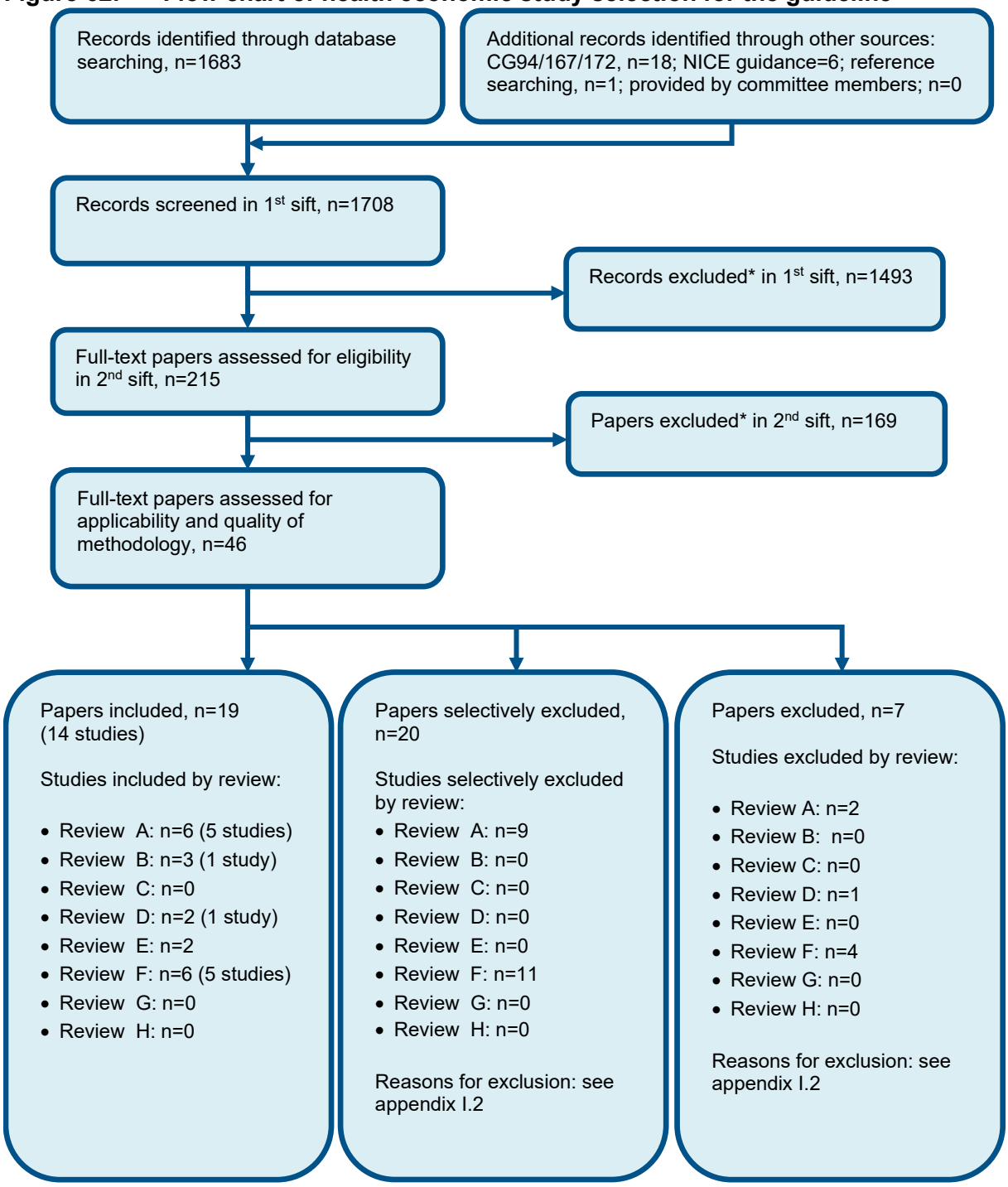
Appendix H: Health economic evidence selection

Figure 62: 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 I: Health economic evidence tables

None.

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 34: Studies excluded from the clinical review

Study	Exclusion reason
Ako 2019[1]	Sub-population of REDUAL
Alexander 2008[2]	Not review population
Alexander 2009[3]	Not review population
Alexander 2011[4]	Not review population
Alexander 2014[5]	Not review population
Amarenco 2014[6]	Not review population
Anand 2018[7]	Not review population
Anastasius 2017[8]	Incorrect study design
Anonymous 2012[9]	Abstract only
Banerjee 2019[10]	Not review population. Incorrect study design
Bastiany 2018[11]	Incorrect study design
Bennaghmouch 2018[12]	Meta-analysis - checked for references
Bhagirath 2018[13]	Incorrect study design
Bosch 2017[14]	Not review population
Brodin 2009[15]	Not review population
Brunetti 2018[16]	Meta-analysis - checked for references
Bunmark 2018[17]	Meta-analysis - checked for references
Cairns 2008[18]	Incorrect study design
Cavallari 2018[21]	Meta-analysis - checked for references
Chi 2018[22]	Bivariate analysis of PIONEER and REDUAL, no usable outcomes

Connolly 2018[24]	Not review population
Dewilde 2009[25]	Not review population
Dewilde 2013[27]	Not review population
Dewilde 2015[26]	Not review population
Eikelboom 2017[28]	Systematic review - checked for reference
Fortuni 2018[29]	Systematic review - checked for references
Franchi 2016[30]	Not review population
Gao 2013[32]	Results not yet published
Gao 2015[31]	Results not yet published
Gibson 2011[34]	Not review population
Gibson 2018[33]	Not review population
Gibson 2019[38]	Not review population
Goette 2016[39]	Not review population
Golwala 2018[40]	Meta-analysis - checked for references
Greenberg 2019[41]	Not review population
Halg 2009[42]	Incorrect interventions
Hess 2015[44]	Not review population
Hoshi 2017[45]	Inappropriate comparison
Jackson 2015[46]	Incorrect study design
Jackson 2016[47]	Inappropriate comparison
Khan 2018[52]	Meta-analysis - checked for references
Khan 2018[51]	Meta-anlaysis - check for references
Korjian 2019[53]	Not review population
Lamy 2019[54]	Not review population
Li 2018[55]	Meta-analysis - checked for references
Liang 2012[56]	Not in English

Lip 2017[58]	Not review population
Lip 2017[57]	Not review population
Lip 2019[59]	Ancillary study of the REDUAL trial that does not address the clinical question
Lopes 2019[61]	Network meta-analysis – incorrect population. This network meta-analysis did not have a threshold for the proportion of ACS in the study populations. The committee agreed a threshold of >60% ACS. One of the studies included in Lopes 2019 has been excluded from this evidence review as proportion of ACS is <60%.
Lou 2018[63]	Meta-analysis - checked for references
Lu 2015[64]	Results not yet published
Maegdefessel 2008[65]	Incorrect study design
Massie 2009[66]	Incorrect interventions
Matsumura-Nakano 2019[67]	Not review population
Mega 2009[68]	Not review population
Mo 2018[69]	Meta-analysis - references checked
Nijenhuis 2016[71]	Results not yet publishes
Ogawa 2013[72]	Not review population
Ohman 2017[73]	Not review population
Oldgren 2011[74]	Not review population
Özdemir 2017[76]	Not in English
Palla 2019[77]	Meta-analysis - references checked
Pandor 2016[78]	Incorrect study design
Patti 2018[79]	Incorrect study design
Povsic 2016[80]	Not review population
Sambola 2013[81]	Results not yet published
Schwalm 2010[82]	Not review population
Shin 2018[83]	Meta-analysis - references checked
Steg 2011[84]	Incorrect interventions

Tan 2008[85]	Not in English
Vafaey 2018[86]	No outcomes
Vranckx 2018[87]	Design and rationale only, full paper not yet publishes
Windecker 2017[89]	Study terminated, no results
Yasuda 2018[90]	Results not yet published
Yuan 2018[91]	Meta-analysis - references checked
Zhang 2019[92]	Meta-analysis - references checked

J.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 35: Studies excluded from the health economic review

Reference	Reason for exclusion
None.	

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