National Institute for Health and Care Excellence

Consultation

Acute coronary syndrome

Network meta-analysis: Anti-platelets for managing unstable angina or NSTEMI or STEMI

NICE guideline <number>

Network meta-analysis report

February 2020

Draft for Consultation

This guideline was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Contents

1 Introduction

Network meta-analysis (NMA) is a statistical technique that allows simultaneous pooling of data for three or more interventions when the available evidence forms a connected network of intervention comparisons from RCTs (for example: evidence from trials comparing interventions A vs B, trials of B vs C and trials of C vs A).[5, 9, 15] This enables both direct evidence (for example A vs B trials for the AvB comparison) and indirect evidence (for example A vs C and B vs C trials provide an indirect estimate of AvB) to be pooled. NMA combines all the available data simultaneously into a single set of treatment effects that provide a unique ordering of intervention effectiveness, whilst respecting the randomisation in the included RCTs. The resulting estimates are therefore easier to interpret than a series of pairwise comparisons, enables ranking of the interventions, and because both direct and indirect evidence is pooled treatment effects are more precisely estimated (have greater statistical power). NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all of the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we have to be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by measuring statistical heterogeneity, and also by checking if the direct and indirect estimates are in agreement when there are loops of evidence in the network (eg an ABC triangle of evidence). The analysis provides estimates of relative effects (with 95% credible intervals) for each intervention compared to a reference intervention (in this case the reference intervention was clopidogrel in combination with aspirin) as well as estimates of all pairwise comparisons. In addition, for a given assumed “baseline effect” on the reference intervention, we can obtain absolute effects for all interventions. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Having a single set of intervention effects that takes into account all the available evidence also facilitates cost effectiveness analysis.

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

Study selection

A systematic review of RCTs comparing any of clopidogrel + aspirin, prasugrel + aspirin or ticagrelor + aspirin in an ACS population was undertaken for the guideline. Studies identified in this review were considered for inclusion in the NMA. The full details for the dual anti-platelets evidence review can be found in the evidence review on dual anti-platelet therapy.

We performed NMAs that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence.

1.1 Population

The review and pairwise meta-analyses considered all ACS data together but also analysed data by the following subgroups:

- STEMI + revascularisation;
- UA/NSTEMI + revascularisation; and
- UA/NSTEMI + no revascularisation.

The committee agreed that comparisons for the overall ACS population were most relevant on the basis of the mechanism of acute coronary syndromes and so it was reasonable to assume relative treatment effects may be similar across populations. However, STEMI is a medical emergency, requiring immediate treatment, so with well-established differential onsets of action of clopidogrel, prasugrel and ticagrelor, it is conceivable that this may impact their relative clinical effectiveness in STEMI patients. Therefore to ensure evidence suggesting any potential differential effects was not omitted, the committee agreed to also consider stratification by condition (i.e. STEMI or UA/NSTEMI) and management approach (i.e. with or without revascularisation) in pairwise meta-analyses.

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

1.2 Outcome measures

30 day outcomes

Five outcomes were selected for the NMA. All of the five outcomes were deemed as critical outcomes for decision making by the committee and/or important for incorporation in the cost effectiveness analysis:

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

The pairwise review found outcome data at different time points including at 30 days and 1 year – these were analysed as separate outcomes in the pairwise meta-analyses. One

potential issue with this approach was that some of the very large RCTs studies did not fully reported outcomes at 30 days (only 1 year) – for example they were only available in a particular subgroup such as UA/NSTEMI. The committee agreed that 30 day data should be requested where not reported for all subgroups for inclusion in the NMA.

1 year outcome data

Following the publication of ISAR-REACT 5 trial data,[23] there was a connected network available for all-cause mortality, reinfarction, stroke and major bleeding at 1 year, therefore the potential to conduct an NMA for 1 year outcomes was explored. To test if there were potential inconsistencies between estimates of relative treatment effects at 1 year, the Bucher test for inconsistency[4] was conducted. As the pairwise meta-analyses for these outcomes at 1 year used a fixed effects model, the Bucher test for inconsistency[4] was deemed appropriate to test for inconsistency as the results from this test would agree with the results from a node-splitting approach. The Bucher test showed that there was inconsistency in 3 of the 4 outcome analyses. The studies and their outcome data was checked for accuracy in case this explained inconsistency. These checks did not identify any inaccuracies in the data used in the Bucher test.Therefore, it was deemed not apprppriate an NMA was not appropriate for the1 year outcomes and was therefore not conducted. The committee therefore considered the pairwise data for the decision-making and took into the account the inconsistency identified. Health economic modelling also explored the implications of this inconsistency (seen in Evidence Review A and the Health Economic Modelling Report). The Bucher test is testing the null hypothesis that Omega is equal to zero, where Omega equals the difference between the direct logodds of A versus B and indirect logodds of A versus B. A breakdown of the results from this test are shown in Appendix B:.

It is noted that the assessment of MI and bleeding varied between studies. The approach taken for the NMA was the same as that agreed with the committee for the pairwise meta analyses. MI would be pooled irrespective of definition. Bleeding was pooled using the most relevant definition of bleeding reported in the study based on a hierarchy agreed by the committee (see protocol).

1.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials and included in the clinical systematic review already presented in the evidence review on dual anti-platelet therapy. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

For all of the five NMAs, the following interventions were included:

Clopidogrel in combination with aspirin (clopidogrel + aspirin)
Prasugrel in combination with aspirin (prasugrel + aspirin)
Ticagrelor in combination with aspirin (ticagrelor + aspirin)

As per the protocol, interventions must have been initiated as part of acute management: for example peri-procedural, or during index hospitalisation. It is noted that the loading dose of clopidogrel varied between studies. Of the 11 studies which had a trial arm of clopidogrel in combination with aspirin, 54% reported a loading dose of 300mg, the remaining studies reported a loading dose of 600mg. The committee agreed that this should interact with the relative treatment effects.

2 Statistical methods

2.1 Synthesis methods

A Bayesian framework is used to estimate all parameters, using Markov chain Monte Carlo simulation methods implemented in WinBUGS 1.4.3.[16, 17] A generalised linear model with a binomial likelihood and logit link was fitted for all outcom.es assessed. Non-informative Normal(0,10000) priors were assigned to the trial-specific baseline and treatments effects (log odds ratios), while a Uniform(0,5) prior was assigned to the between-study standard deviation in the random effects models.[9] Each analysis was run with 3 chains, each with a different set of initial values, to check that the model had converged through the mixing of chains via history plots.Convergence was also assessed using the Brooks-Gelman-Rubin diagnostic plot[3, 11] and was satisfactory by 60,000 simulations for all outcomes. A further sample of 60,000 iterations post-convergence was obtained on which all reported results were based.

We assessed the goodness of fit of the model by calculating the mean of the posterior distribution of the residual deviance. If this is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

Studies with zero or 100% events in all arms were excluded from the analysis because these studies provide no evidence on relative effects.[9] For studies with zero or 100% events in one arm only, we planned to analyse the data without continuity corrections where computationally possible. Where this was not possible (for the outcomes: all-cause mortality, new MI, stroke and minor bleeding) we used a continuity correction where we added 0.5 to both the number of events and 1 to the total randomised, which has shown to perform well when there is an approximate 1:1 randomisation ratio across intervention arms.[25]

2.1.1 Between study heterogeneity

When considering models for network meta-analysis (NMA), there are several aspects of the data that will impact the choice of parameters included in the model. To assess the validity of an NMA it is essential to assess the extent of heterogeneity and inconsistency. Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts.[10]

A fixed effects NMA model is the simplest model available to estimate the effects of interventions separately while simultaneously synthesizing all available evidence. This model assumes no heterogeneity between trials within each treatment contrast. In other words, all trials are estimating the same treatment effect, regardless of any differences in the conduct of the trials, populations, or treatments (i.e., administration or dose). A random effects NMA model relaxes this assumption accounting for any differences in treatment effects between trials that are beyond chance by estimating and accounting for the between-study standard deviation. When critiquing NMA models, it is good practice to assess and compare the fit (i.e., the posterior residual deviance) and DIC of both fixed and random effects models, as a meaningful improvement observed in the random effects model of at least 3 points[24] may provide evidence of potential between-study heterogeneity.

2.1.2 Baseline model and data

The baseline risk is defined as the (absolute) risk of achieving the outcome of interest for patients receiving the reference intervention (clopidogrel+aspirin) in the population of interest. Relative effects estimated from the NMA can be applied to the absolute baseline risk to obtain absolute risks under each intervention in the population of interest (see section 2.2). This allows us to convert the results of the NMA, which are estimated as odds ratios, into risk

ratios for easier interpretation. Two studies (PLATO trial and TRITON trial) were used to inform the baseline, which are the studies the committee agreed are most relevant to the UK population; the risk of events are reported in Table 1. We fitted fixed and random single-arm meta-analysis models to the TRITON and PLATO studies for each outcome. Where a fixed effect model gave an adequate fit to the data, the pooled estimate was used. Where there was evidence of heterogeneity, we performed a sensitivity analysis where the TRITON or PLATO estimates were taken individually as the baseline effect, and the resulting sets of relative risks were compared.

Table 1: Risk of events reported in the PLATO and TRITON trials that informed baseline risk - for the clopidogrel + aspirin arm

	TRITON		PLATO	
Outcome	Number of events / Total randomised	Proportion	Number of events / Total randomised	Proportion
All-cause mortality at 30 days	45/1765	2.55%	212/9186*	2.31%
New myocardial infarction at 30 days	123/1765	6.97%	165/9186*	1.80%
Stroke at 30 days	16/1765	0.91%	43/9186*	0.47%
Major bleeding at 30 days	23/1765	1.30%	642/9186*	6.99%
Minor bleeding at 30 days	57/1765	3.23%	-	

**unpublished data requested and received from authors*

2.2 Summary measures and reference treatment

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review of dual anti-platelet therapy.

In the NMA, data were pooled as log odds ratios. To facilitate comparison with the results of the pairwise MA, we converted the log odds ratios into relative risks as follows. Assuming a baseline probability of effect in the population of interest P[b] (as described above in Section 2.1.2), the relative risks were calculated as:

RR[k] = P[k]/P[b], where logit(P[k]) = log(OR[k]) + logit(P[k]) for treatment k

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale. It also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative risk compared to control group. Due to the skewness of the data, the NMA relative risks and rank results are reported as medians rather than means to give a more accurate representation of the 'most likely' value.

In the cost effectiveness analysis, odds ratios were used instead of relative risks. The analysis modelled people undergoing PCI, and those with STEMI and UA/NSTEMI were modelled separately. As a result, real world baseline risks for the clopiodgrel and aspirin arm were identified for the STEMI with PCI and UA/NSTEMI with PCI populations and were used in the economic model. Therefore it was appropriate to use the odds ratios from the NMA

instead of relative risks. These odds ratios are presented in **Error! Reference source not found.**.

2.3 Methods of assessing inconsistency

A key assumption behind NMA is that the evidence in the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes relating to differences between the trials included in terms of their clinical or methodological characteristics that interact with the relative intervention effects.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by more narrowly defining inclusion criteria.

Inconsistency was assessed by comparing the chosen consistency model (fixed or random effects) to an “inconsistency”, or unrelated mean effects, model.[10] The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 or more treatments that are informed by at least 3 distinct trials.[26]

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess the goodness of fit of each model.[24] Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point).[24] In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the deviance information criterion (DIC). This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity.[24] Lower values are preferred and typically differences of at least 3 points are considered meaningful.[24]

2.4 Assessing clinical importance

The credible intervals of the treatment effects were inspected to determine if there was statistical evidence of a difference between treatments, with no overlap in credible intervals indicating evidence of a difference between treatment effects. If a statistical difference was identified, then the magnitude of the difference was considered meaningful if it was larger than the minimal important differences (MIDs). For dichotomous outcomes, the MIDs were taken to be a risk ratio (relative risk) of 0.8 and 1.25 (more information in Methods chapter).

3 Results

3.1 All-cause mortality at 30 days

3.1.1 Network and data

15 studies were identified as reporting outcome data for all-cause mortality at 30 days. After excluding studies that reported zero events in all arms, since they do not contribute evidence to the NMA.[9] 14 studies involving the 3 interventions were included in the all-cause mortality network. The network can be seen in Figure 1 and the trial data for each of the studies included in the NMA are presented in Table 2.

Figure 1: Network diagram for all-cause mortality at 30 days

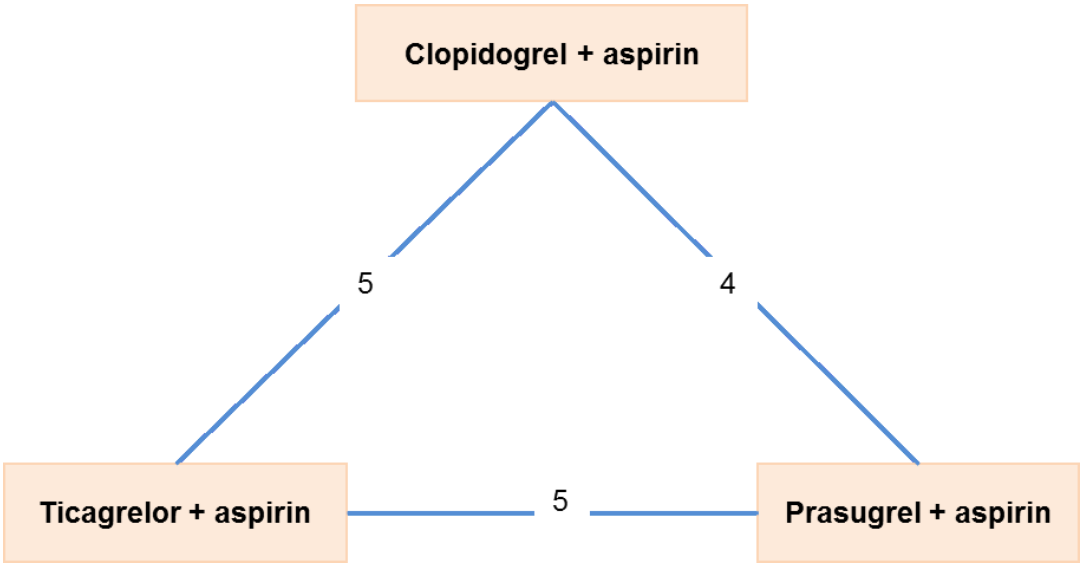


Table 2: Study data for all-cause mortality at 30 days network meta-analysis

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Dehghani 2017[8]	Ticagrelor + aspirin	Clopidogrel + aspirin	1	76	3	68
Cannon 2007 (DISPERSE-2)[6]	Ticagrelor + aspirin	Clopidogrel + aspirin	6	334	2	327
Wallentin 2009 (PLATO)[27]*	Ticagrelor + aspirin	Clopidogrel + aspirin	179	9235	212	9186
Wang 2019[29]	Ticagrelor + aspirin	Clopidogrel + aspirin	3	150	6	148
Jing 2016[13]	Ticagrelor + aspirin	Clopidogrel + aspirin	1	94	1	94
Roe 2012 (TRILOGY)[22]*	Prasugrel + aspirin	Clopidogrel + aspirin	39	4663	44	4663
Zeymer 2015 (ETAMI)[30]	Prasugrel + aspirin	Clopidogrel + aspirin	1	31	1	31
Montalescot 2009 (TRITON)[18]	Prasugrel + aspirin	Clopidogrel + aspirin	28	1769	45	1765
Dasbiswas 2013[7]	Prasugrel + aspirin	Clopidogrel + aspirin	2	111	1	109

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Alexopoulous 2012[1]	Prasugrel + aspirin	Ticagrelor + aspirin	3	27	1	28
Motovska 2016 (PRAGUE18)[19]	Prasugrel + aspirin	Ticagrelor + aspirin	14	634	16	596
Parodi 2013 (RAPID I)[21]	Prasugrel + aspirin	Ticagrelor + aspirin	0	25	2	25
Parodi 2014 (RAPID II)[20]	Prasugrel + aspirin	Ticagrelor + aspirin	1	25	1	25
Laine 2014[14]	Prasugrel + aspirin	Ticagrelor + aspirin	0	50	1	50

n = number of participants

**unpublished data requested and received from authors*

3.1.2 Results of network meta-analysis

Table 3 summarises the results of the pairwise meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA (this is from a fixed effects model, which was chosen on the basis of model fit (see section 3.1.3)) in terms of risk ratios for every possible treatment comparison. Table 4 presents summary statistics for the three interventions included in the network, including the rank of the intervention, probability of the intervention being the best and mean probability of an event.

Table 3: Risk ratios for all-cause mortality at 30 days; direct pairwise meta-analysis results and NMA results

Intervention	Comparison	Pairwise fixed effects model - mean (95% confidence intervals)	NMA fixed effects model (with pooled baseline estimate)- median (95% credible intervals)
Ticagrelor + aspirin	Clopidogrel + aspirin	0.84 (0.70, 1.02)	0.85 (0.70, 1.02)
Prasugrel + aspirin		0.83 (0.64, 1.06)	0.81 (0.64, 1.02)
Prasugrel + aspirin	Ticagrelor + aspirin	0.91 (0.50, 1.67)	0.96 (0.72, 1.26)

Table 4: Intervention rank and mean probability of event– all-cause mortality [results are based on baseline results informed by a pooled estimate of TRITON and PLATO from a fixed effect model]

	Probability of death by day 30 – posterior mean (95% credible intervals) and per 1000 patients	Intervention rank - median (95% CrIs)	Probability intervention is best (%)
Clopidogrel + aspirin	0.0235 (0.0208, 0.0264) 24 per 1000 patients	3 (2,3)	0%
Ticagrelor + aspirin	0.0199 (0.0159, 0.0247) 20 per 1000 patients	2 (1,3)	38%
Prasugrel + aspirin	0.0191 (0.0146, 0.0246)	1 (1,3)	62%

	Probability of death by day 30 – posterior mean (95% credible intervals) and per 1000 patients	Intervention rank - median (95% CrIs)	Probability intervention is best (%)
	19 per 1000 patients		

3.1.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the clopidogrel in combination with aspirin arms of the TRITON and PLATO studies. As seen in Table 5, the fixed effects baseline model had a DIC of 15.17 compared to 16.45 for the random effects baseline model. The fixed effects baseline model was therefore the preferred model and used to estimate the baseline effect for combination with the NMA relative effects to obtain absolute probabilities and relative risks outputs.

There was no evidence of heterogeneity in the NMA model, as there was a slightly better fit (ResDev) for the fixed effects NMA model than for the random effects model. In addition, the DIC was a lower.

An inconsistency model was run and the model fit statistics were as seen in Table 5. The NMA model has a slightly smaller DIC suggesting that there is no evidence of inconsistency, a conclusion which is supported by comparing risk ratios from the pairwise and NMA models (Table 3).

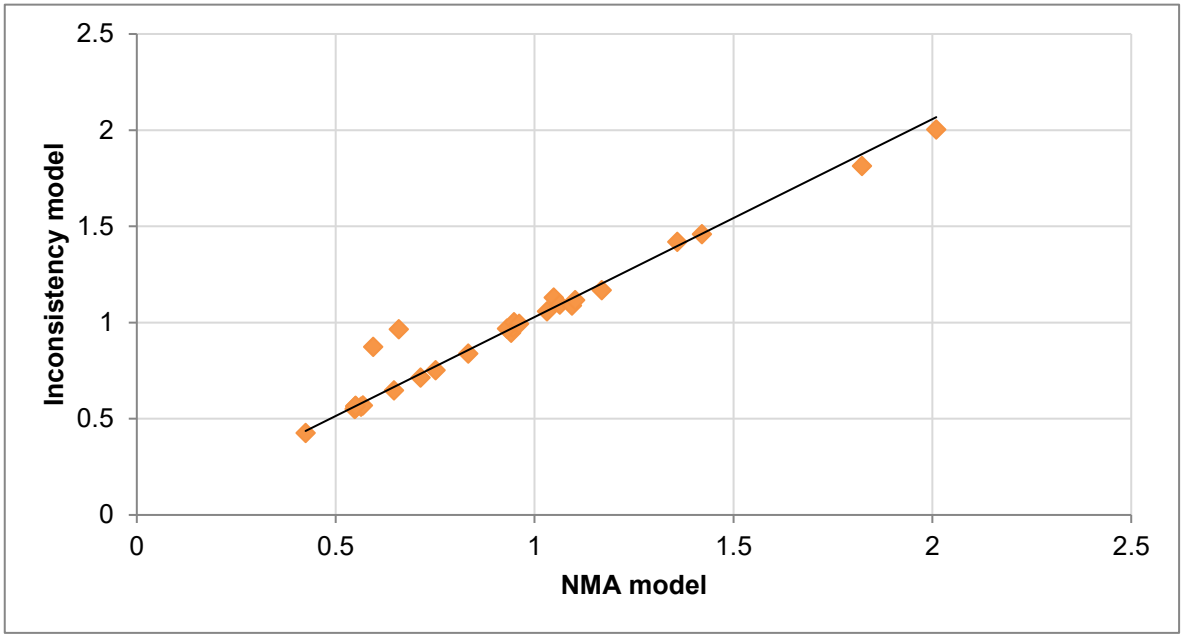
Figure 2 presents the contributions to the posterior mean of the deviances for each data-point for the inconsistency model against that for the consistency NMA model. There is no evidence of inconsistency, as there are no points notably below the line of equality, which would be indicative of data better predicted by the inconsistency model.

Table 5: Model fit statistics – all-cause mortality

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
Baseline models[(a)]		
Fixed effects	15.17	1.4
Random effects	16.45	1.8
Relative effect models[(b)]		
NMA Fixed effects	134.21	24.8
NMA Random effects	136.03	25.1
Inconsistency model [FE]	136.14	25.8

(a) Number of data points in baseline model (n=2)
(b) Number of data points in the NMA and inconsistency models (n=28)

Figure 2: Posterior mean of the contribution to the posterior mean residual deviance of the inconsistency model vs. the consistency model – all-cause mortality



3.2 New myocardial infarction at 30 days

3.2.1 Network and data

13 studies were identified as reporting outcome data for new myocardial infarction (MI) at 30 days. After excluding studies that reported zero events in all arms, 11 studies involving the 3 interventions were included in the new MI network. The network can be seen in Figure 3 and the trial data for each of the studies included in the NMA are presented in

Table **6**.

Figure 3: Network diagram for new myocardial infarction at 30 days

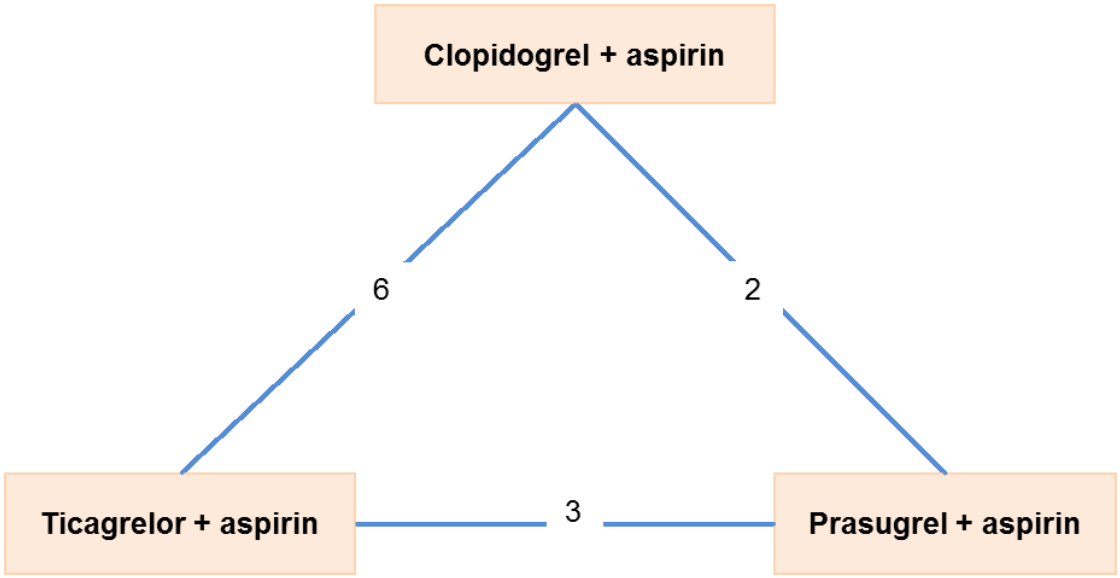


Table 6: Study data for new myocardial infarction at 30 days network meta-analysis

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Cannon 2007 (DISPERSE-2)[6]	Ticagrelor + aspirin	Clopidogrel + aspirin	7	334	11	327
Dehghani 2017[8]	Ticagrelor + aspirin	Clopidogrel + aspirin	0	76	1	68
Wang 2016b[28]	Ticagrelor + aspirin	Clopidogrel + aspirin	1	87	5	87
Wang 2019[29]	Ticagrelor + aspirin	Clopidogrel + aspirin	3	150	7	148
Wallentin 2009 (PLATO)[27]*	Ticagrelor + aspirin	Clopidogrel + aspirin	121	9235	165	9186
Han 2019[12]	Ticagrelor + aspirin	Clopidogrel + aspirin	2	60	4	60
Roe 2012 (TRILOGY)[22]*	Prasugrel + aspirin	Clopidogrel + aspirin	74	4663	78	4663
Montalescot 2009 (TRITON)[18]	Prasugrel + aspirin	Clopidogrel + aspirin	87	1769	123	1765
Motovska 2016 (PRAGUE18)[19]	Prasugrel + aspirin	Ticagrelor + aspirin	8	634	7	596
Parodi 2013 (RAPID I)[21]	Prasugrel + aspirin	Ticagrelor + aspirin	1	25	0	25
Laine 2014[14]	Prasugrel + aspirin	Ticagrelor + aspirin	1	50	0	50

n = number of participants

**unpublished data requested and received from authors*

3.2.2 Results of network meta-analysis

Table 7 summarises the results of the pairwise meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of

the NMA (this is from a fixed effects model, which was chosen on the basis of model fit (see section 3.2.3)) in terms of risk ratios for every possible treatment comparison. Table 8 presents summary statistics for the three interventions included in the network, including the rank of the intervention, probability of the intervention being the best and mean probability of an event.

Table 7: Risk ratios for new myocardial infarction at 30 days; direct pairwise meta-analysis results and NMA results

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

Table 8: Intervention rank and mean probability of event – new MI [results are based on baseline results informed by a pooled estimate of TRITON and PLATO from a fixed effect model]

	Probability of new MI by day 30 – posterior mean (95% credible intervals) and per 1000 patients	Intervention rank – median (95% CrIs)	Probability intervention is best (%)
Clopidogrel + aspirin	0.184 (0.0000695, 0.951) 184 per 1000 patients	3 (3,3)	0%
Ticagrelor + aspirin	0.157 (0.0000477, 0.930) 157 per 1000 patients	1 (1,2)	86%
Prasugrel + aspirin	0.168 (0.0000554, 0.940) 168 per 1000 patients	2 (1,2)	14%

3.2.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the clopidogrel in combination with aspirin arms of the TRITON and PLATO studies. As seen in Table 9, the fixed effects baseline model had a DIC of 133.54 compared to 17.51 for the random effects baseline model. The random effects baseline model was therefore the preferred model and used to estimate the baseline effect for combination with the NMA relative effects to obtain absolute probabilities and relative risks outputs.

There was no evidence of heterogeneity in the NMA, as both models fit the data well, and there were no meaningful differences in the fit (ResDev) or DIC between the fixed and random effects NMA models. The simpler, fixed effect model was thus chosen.

An inconsistency model was run and the model fit statistics were as seen in Table 9. The NMA has a slightly smaller mean residual deviance and DIC suggesting there is no evidence of inconsistency, a conclusion which is supported by comparing risk ratios from the pairwise and NMA models Table 7.

(a) Number of data points in baseline model (n=4)

(b) Number of data points in the NMA and inconsistency models (n=22)

Figure 4 presents the contributions to the posterior mean of the deviances for each data-point for the inconsistency model against that for the consistency NMA model. There is no evidence of inconsistency, as there are no data points notably predicted better by the inconsistency model compared to the NMA model.

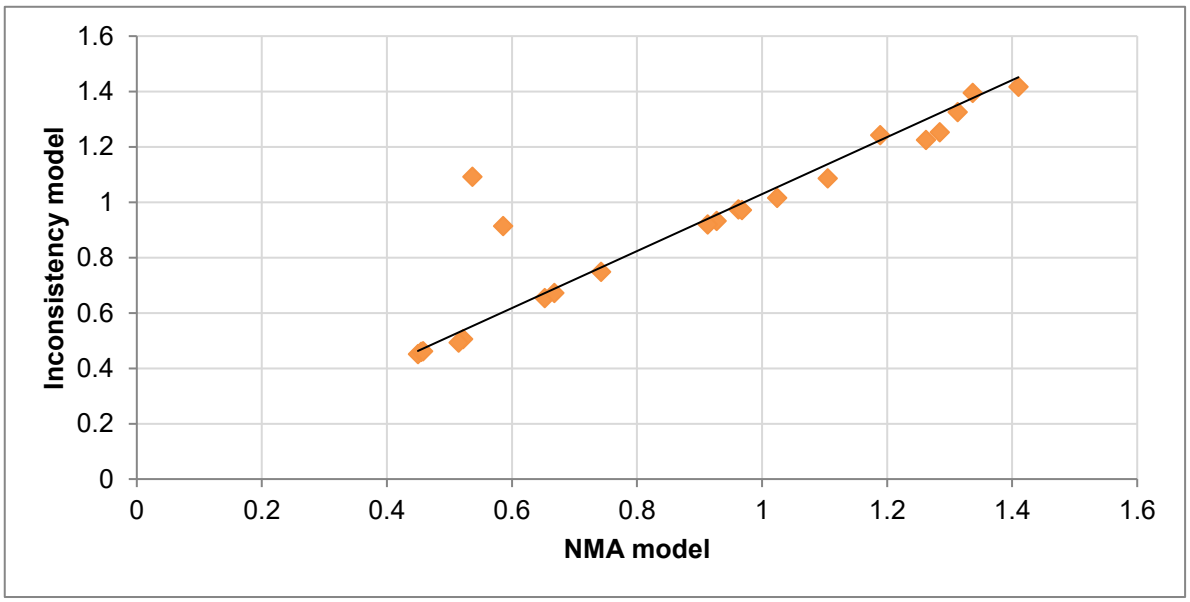
Table 9: Model fit statistics – new myocardial infarction

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
Baseline models		
Fixed effects	133.54	119.0
Random effects	17.51	2.0
Relative effect models		
NMA Fixed effects	115.70	19.3
NMA Random effects	116.70	18.2
Inconsistency model [FE]	117.56	20.2

(c) Number of data points in baseline model (n=4)

(d) Number of data points in the NMA and inconsistency models (n=22)

Figure 4: Posterior mean of the contribution to the posterior mean residual deviance of the inconsistency model vs. the consistency model – new myocardial infarction



3.2.4 Sensitivity analysis

The lower total posterior residual deviance (ResDev) and DIC in the random effects baseline model indicated that there was some heterogeneity in our base-care analysis, between the baseline effects estimated in TRITON and PLATO (Table 9). As such, we used the effect estimated in the PLATO study individually and the effect estimated in TRITON individually, as part of a sensitivity analysis. There were some differences observed between the NMA model outputs for the probability of new MI by day 30 with the PLATO providing lower values (

Table 11). However, there are no observed differences in relative risks (Table 10).

Table 10: Relative risk for sensitivity analysis (PLATO and TRITON - individually) – new MI

Intervention	Comparator	FE Relative Risks (95% CrIs)	
		PLATO	TRITON
Ticagrelor + aspirin	Clopidogrel + aspirin	0.68 (0.55, 0.85)	0.70 (0.57, 0.85)
Prasugrel + aspirin		0.80 (0.65, 0.98)	0.81 (0.66, 0.98)
Prasugrel + aspirin	Ticagrelor + aspirin	1.17 (0.88, 1.56)	1.16 (0.88, 1.53)

Table 11: Mean probability of event following base analysis (PLATO) and sensitivity analysis (TRITON) – new MI

Intervention	Probability of new MI by day 30 - mean (and standard error)	
	PLATO	TRITON
Clopidogrel + aspirin	0.0180 (0.00140) 18 per 1000 patients	0.0697 (0.00611) 70 per 1000 patients
Ticagrelor + aspirin	0.0124 (0.00167) 12 per 1000 patients	0.0487 (0.00676) 49 per 1000 patients
Prasugrel + aspirin	0.0145 (0.00189) 15 per 1000 patients	0.0566 (0.00757) 56 per 1000 patients

3.3 Stroke at 30 days

3.3.1 Network and data

10 studies were identified as reporting outcome data for stroke at 30 days. After excluding studies that reported zero events in all arms, 8 studies involving the 3 interventions were included in the stroke network. The network can be seen in Figure 5 and the trial data for each of the studies included in the NMA are presented in Table 12.

Figure 5: Network diagram for stroke at 30 days

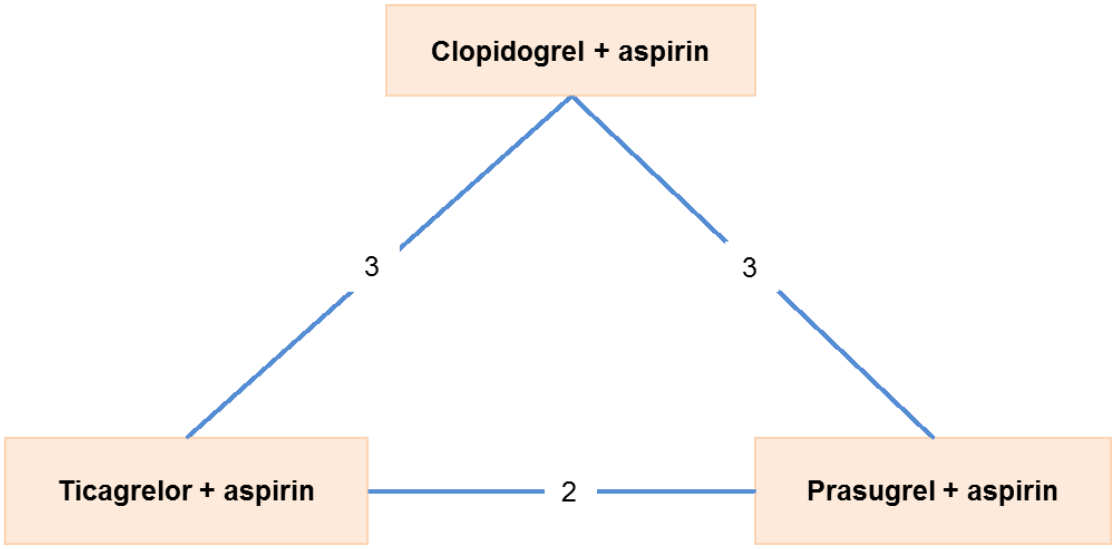


Table 12: Study data for stroke at 30 days network meta-analysis

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Cannon 2007 (DISPERSE-2)[6]	Ticagrelor + aspirin	Clopidogrel + aspirin	2	334	1	327
Wang 2016b[28]	Ticagrelor + aspirin	Clopidogrel + aspirin	2	87	2	87
Wallentin 2009 (PLATO)[27]*	Ticagrelor + aspirin	Clopidogrel + aspirin	57	9235	43	9186
Roe 2012 (TRILOGY) [22]*	Prasugrel + aspirin	Clopidogrel + aspirin	12	4663	11	4663
Montalescot 2009 (TRITON)[18]	Prasugrel + aspirin	Clopidogrel + aspirin	7	1769	16	1765
Dasbiswas 2013[7]	Prasugrel + aspirin	Clopidogrel + aspirin	1	93	1	96
Bonello 2015[2]	Prasugrel + aspirin	Ticagrelor + aspirin	1	107	0	106
Motovska 2016 (PRAGUE18)[19]	Prasugrel + aspirin	Ticagrelor + aspirin	2	634	1	596

n = number of participants

**unpublished data requested and received from authors*

3.3.2 Results of network meta-analysis

Table 13 summarises the results of the pairwise meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA (this is from a fixed effects model, which was chosen on the basis of model fit (see section 3.3.3)) in terms of risk ratios for every possible treatment comparison. Table 14 presents summary statistics for the three interventions included in the network, including the rank of the intervention, probability of the intervention being the best and mean probability of an event.

Table 13: Risk ratios for stroke at 30 days; direct pairwise meta-analysis results and NMA results

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

Table 14: Intervention rank and mean probability of event – stroke [results are based on baseline results informed by a pooled estimate of TRITON and PLATO from a fixed effect model]

	Probability of stroke by day 30 - posterior mean (95% credible intervals) and per 1000 patients	Intervention rank - median (95% CrIs)	Probability intervention is best (%)
Clopidogrel + aspirin	0.00539 (0.00414, 0.00690) 5 per 1000 patients	2 (1,3)	20%
Ticagrelor + aspirin	0.00686 (0.00425, 0.0105) 7 per 1000 patients	3 (1,3)	3%
Prasugrel + aspirin	0.00452 (0.00234, 0.00787) 5 per 1000 patients	1 (1,3)	77%

3.3.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the clopidogrel in combination with aspirin arms of the TRITON and PLATO studies. As seen in Table 15, the random effects baseline model fit the data better compared to the fixed effects baseline model. The random effects baseline model was therefore the preffered model and used to estimate the baseline effect for combination with the NMA relative effects to obtain absolute probabilities and relative risks outputs.

There was no evidence of heterogeneity in the NMA model, as there were no meaningful differences in fit or DIC betweenthe fixed and random effects NMA modelsThe simpler, fixed effect NMA model was therefore preferred.

An inconsistency model was run and the model fit statistics were as seen in Table 15. The difference in the DIC is small (<3) which suggests that there is no evidence inconsistency in the network, a conclusion which is supported by comparing risk ratios from the pairwise and NMA models (Table 13).

(a) However, Number of data points in baseline model (n=4)
(b) Number of data points in the NMA and inconsistency models (n=16)

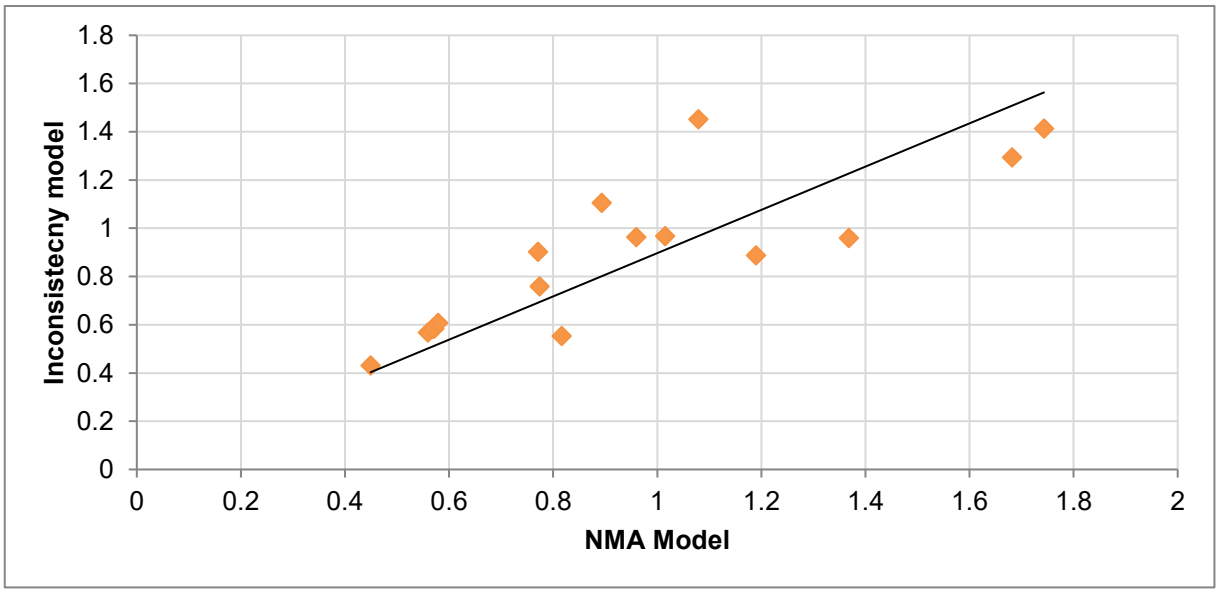
Figure 6 which presents the posterior mean of the deviances of the consistency NMA model versus the posterior mean of the deviances of the inconsistency model shows there are some data points better predicted by the inconsistency model (below the line of equality), demonstrating some evidence of inconsistency.

Table 15: Model fit statistics – stroke

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
Baseline models		
Fixed effects	16.81	5.6
Random effects	14.39	2.1
Relative effect models		
NMA Fixed effects	75.41	15.0
NMA Random effects	76.53	14.2
Inconsistency model [FE]	75.23	14.0

(c) Number of data points in baseline model (n=4)
(d) Number of data points in the NMA and inconsistency models (n=16)

Figure 6: Posterior mean of the contribution to the posterior mean residual deviance of the inconsistency model vs. the consistency model - stroke



3.3.4 Sensitivity analysis

The lower total posterior residual deviance (ResDev) and DIC in the random effects baseline model indicated that there was some heterogeneity between the baseline effects estimated in TRITON and PLATO (Table 15). As such, we used the effect estimated in the PLATO study individually and the effect estimated in TRITON individually, as part of a sensitivity analysis. There were some differences observed between the NMA model outputs for the probability of stroke by day 30 with the base analysis providing lower values. (Table 17). However, there are no observed differences in relative risks (Table 16).

Table 16: Relative risk for sensitivity analysis (PLATO and TRITON - individually) – stroke

Intervention	Comparator	FE Relative Risks (95% CrI)	
		PLATO	TRITON
Ticagrelor + aspirin	Clopidogrel + aspirin	1.25 (0.86, 1.82)	1.25 (0.86, 1.81)
Prasugrel + aspirin		0.81 (0.46, 1.39)	0.81 (0.47, 1.39)
Prasugrel + aspirin	Ticagrelor + aspirin	0.65 (0.34, 1.22)	0.65 (0.34, 1.22)

Table 17: Mean probability of event following base analysis (PLATO) and sensitivity analysis (TRITON) – stroke

Intervention	Probability of stroke by day 30 - mean (and standard error)	
	PLATO	TRITON
Clopidogrel + aspirin	0.00468 (0.000722) 5 per 1000 patients	0.00907 (0.00233) 9 per 1000 patients
Ticagrelor + aspirin	0.00597 (0.00149) 6 per 1000 patients	0.0115 (0.00373) 12 per 1000 patients
Prasugrel + aspirin	0.00393 (0.00128) 4 per 1000 patients	0.00761 (0.00296) 8 per 1000 patients

3.4 Major bleeding at 30 days

3.4.1 Network and data

10 studies were identified as reporting outcome data for major bleeding at 30 days. After excluding studies that reported zero events in all arms, 9 studies involving the 3 interventions were included in the major bleeding network. The network can be seen in Figure 7 and the trial data for each of the studies included in the NMA are presented in Table 18.

Figure 7: Network diagram for major bleeding at 30 days

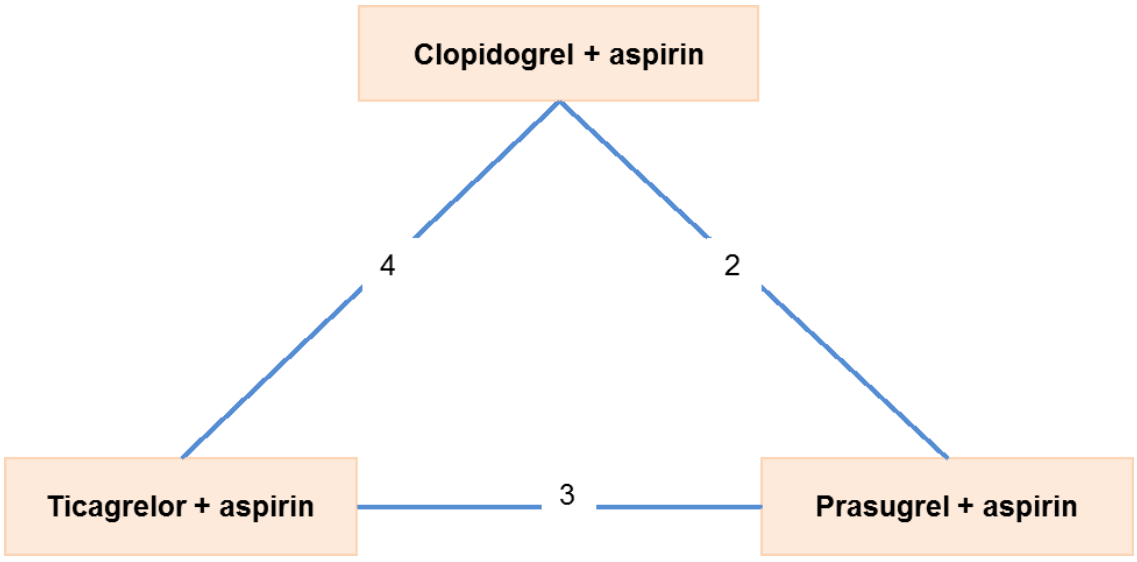


Table 18: Study data for major bleeding at 30 days network meta-analysis

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Cannon 2007 (DISPERSE-2)[6]	Ticagrelor + aspirin	Clopidogrel + aspirin	23	334	22	327
Dehghani 2017[8]	Ticagrelor + aspirin	Clopidogrel + aspirin	2	76	1	68
Wallentin 2009 (PLATO)[27]*	Ticagrelor + aspirin	Clopidogrel + aspirin	645	9235	642	9186
Wang 2019[29]	Ticagrelor + aspirin	Clopidogrel + aspirin	5	150	4	148
Roe 2012 (TRILOGY)[22]*	Prasugrel + aspirin	Clopidogrel + aspirin	7	4663	6	4663
Montalescot 2009 (TRITON)[18]	Prasugrel + aspirin	Clopidogrel + aspirin	17	1769	23	1765
Bonello 2015[2]	Prasugrel + aspirin	Ticagrelor + aspirin	8	107	7	106
Motovska 2016 (PRAGUE18)[19]	Prasugrel + aspirin	Ticagrelor + aspirin	4	634	2	596
Parodi 2014 (RAPID II)[20]	Prasugrel + aspirin	Ticagrelor + aspirin	2	25	1	25

n = number of participants

**unpublished data requested and received from authors*

3.4.2 Results of network meta-analysis

Table 19 summarises the results of the pairwise meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA (this is from a fixed effects model, which was chosen on the basis of model fit (see section 3.4.3)) in terms of risk ratios for every possible treatment comparison. Table 20 presents summary statistics for the three interventions included in the network, including the rank of the intervention, probability of the intervention being the best and mean probability of an event.

Table 19: Risk ratios for major bleeding at 30 days; direct pairwise meta-analysis results and NMA results

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

Table 20: Intervention rank and mean probability of event – major bleeding [results are based on baseline results informed by a pooled estimate of TRITON and PLATO from a fixed effect model]

	Probability of major bleeding by day 30 – posterior mean (standard error) and per 1000 patients	Intervention rank - median, (95% CrIs)	Probability intervention is best (%)
Clopidogrel + aspirin	0.181 (0.0000458, 0.957) 181 per 1000 patients	2 (1,3)	22%
Ticagrelor + aspirin	0.180 (0.0000459, 0.958) 180 per 1000 patients	2 (1,3)	26%
Prasugrel + aspirin	0.180 (0.0000436, 0.956) 180 per 1000 patients	1 (1,3)	52%

3.4.3 Inconsistency and goodness of fit

Both fixed effects and random effects baseline models were fitted to the data from the clopidogrel in combination with aspirin arms of the TRITON and PLATO studies. As seen in Table 21, the fixed effects baseline model had a DIC of 129.91 compared to 17.19 for the random effects baseline model. The random effects baseline model was therefore the preferred model and used to estimate the baseline effect for combination with the NMA relative effects to obtain absolute probabilities and relative risks outputs.

There was no evidence of heterogeneity in the NMA model, as there was a slightly better fit for the fixed effects NMA model than for the random effects model, and the DIC of the former model was smaller. The simpler, fixed effects NMA model was therefore preferred.

An inconsistency model was run and the model fit statistics were as seen in Table 21. The NMA has a slightly smaller DIC suggesting that there is no evidence of inconsistency, a conclusion which is supported by comparing risk ratios from the pairwise and NMA models (Table 19).

(a) Number of data points in baseline model (n=4)
(b) Number of data points in the NMA and inconsistency models (n=18)

Figure 8 presents the posterior mean of the deviances of the inconsistency NMA model versus the posterior mean of the deviances of the consistency model, which shows there are some data points better predicted by the inconsistency model (below the line of equality). However, the deviances for these data-points are all less than 1.2, suggesting only very weak evidence of inconsistency.

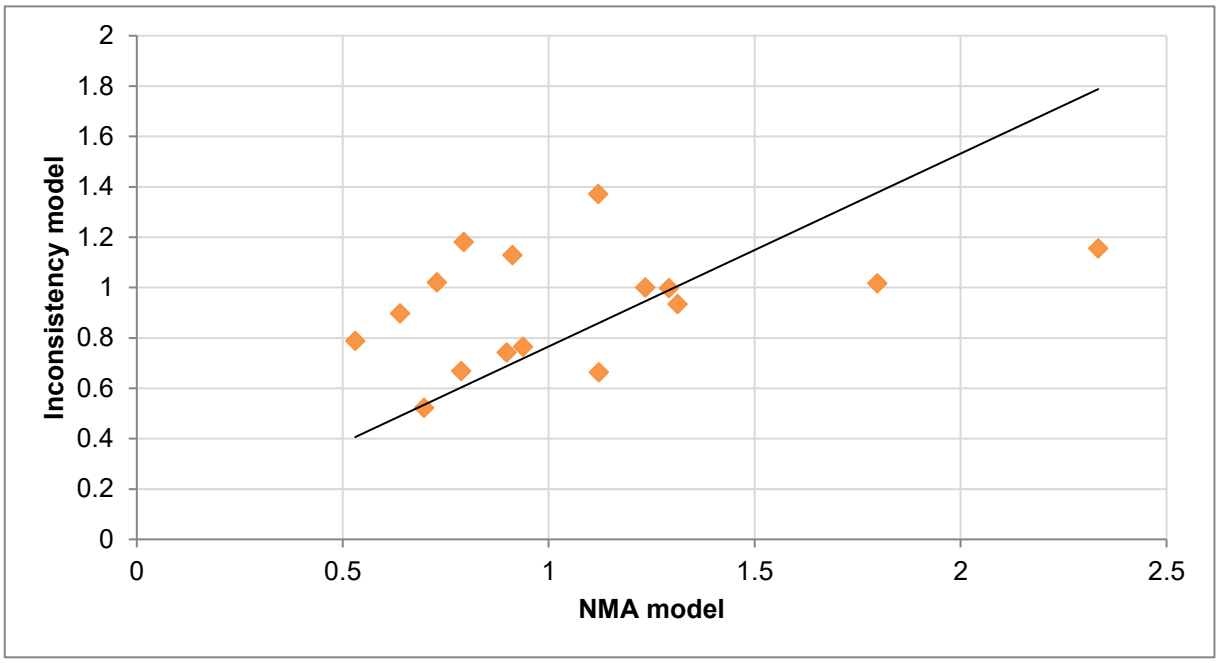
Table 21: Model fit statistics – major bleeding

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
Baseline models		
Fixed effects	129.91	115.7
Random effects	17.19	2.0
Relative effect models		
NMA Fixed effects	96.93	13.5

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
NMA Random effects	98.88	14.1
Inconsistency model [FE]	97.84	13.4

(c) Number of data points in baseline model (n=4)
(d) Number of data points in the NMA and inconsistency models (n=18)

Figure 8: Posterior mean of the contribution to the posterior mean residual deviance of the inconsistency model vs. the consistency model – major bleeding



3.4.4 Sensitivity analysis

The lower total posterior residual deviance (ResDev) and DIC in the random effects baseline model indicated that there was some heterogeneity between the baseline effects estimated in TRITON and PLATO (Table 21). As such, we used the effect estimated in the PLATO study individually and the effect estimated in TRITON individually, as part of a sensitivity analysis. There were some differences observed between the NMA model outputs for the probability of major bleeding by day 30 with the base analysis providing lower values (Table 23). However, there are no observed differences in relative risks (Table 22).

Table 22: Relative risk for sensitivity analysis (PLATO and TRITON - individually) – major bleeding

Intervention	Comparator	FE Relative Risks (95% CrI)	
		PLATO	TRITON
Ticagrelor + aspirin	Clopidogrel + aspirin	1.00 (0.90, 1.10)	1.00 (0.90, 1.11)
Prasugrel + aspirin		0.97 (0.63, 1.47)	0.97 (0.62, 1.51)
Prasugrel + aspirin	Ticagrelor + aspirin	0.97 (0.63, 1.48)	0.97 (0.61, 1.53)

Table 23: Mean probability of event following base analysis (PLATO) and sensitivity analysis (TRITON) – major bleeding

Intervention	Probability of major bleeding by day 30 - mean (and standard error)

	PLATO	TRITON
Clopidogrel + aspirin	0.0699 (0.00266) 70 per 1000 patients	0.0131 (0.00276) 13 per 1000 patients
Ticagrelor + aspirin	0.0698 (0.00451) 70 per 1000 patients	0.01303 (0.00285) 13 per 1000 patients
Prasugrel + aspirin	0.0691 (0.0153) 69 per 1000 patients	0.0129 (0.00411) 13 per 1000 patients

3.5 Minor bleeding at 30 days

3.5.1 Network and data

11 studies were identified as reporting outcome data for minor bleeding at 30 days. After excluding studies that reported zero events in all arms, 10 studies involving the 3 interventions were included in the minor bleeding network. The network can be seen in Figure 9 and the trial data for each of the studies included in the NMA are presented in Table 24.

Figure 9: Network diagram for minor bleeding at 30 days

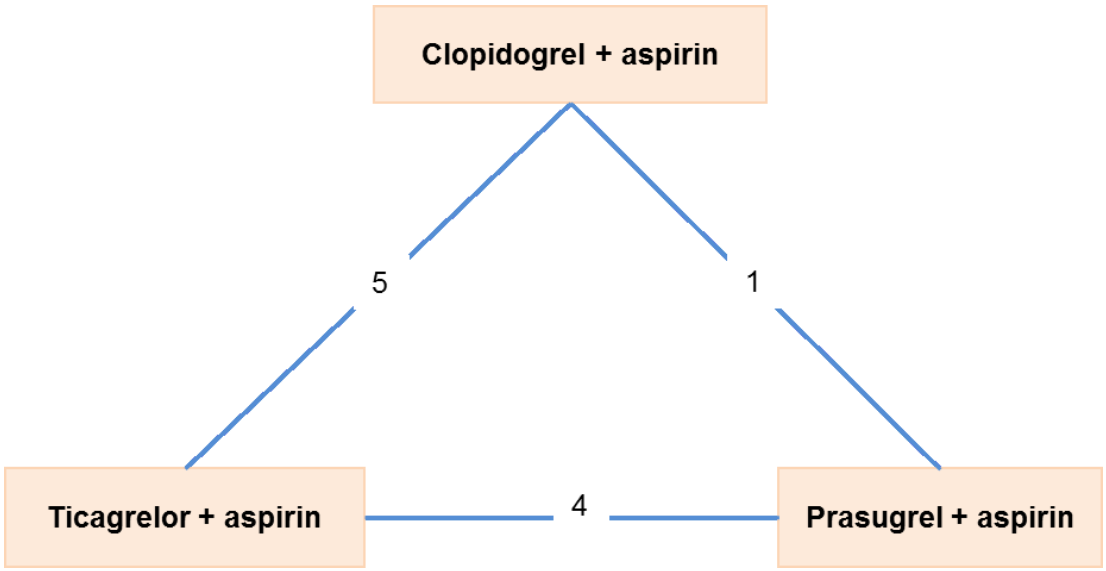


Table 24: Study data for minor bleeding at 30 days network meta-analysis

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
Cannon 2007 (DISPERSE-2)[6]	Ticagrelor + aspirin	Clopidogrel + aspirin	9	334	4	327
Dehghani 2017[8]	Ticagrelor + aspirin	Clopidogrel + aspirin	9	76	5	68
Han 2019[12]	Ticagrelor + aspirin	Clopidogrel + aspirin	3	60	4	60
Wang 2019[29]	Ticagrelor + aspirin	Clopidogrel + aspirin	15	150	10	148
Jing 2016[13]	Ticagrelor + aspirin	Clopidogrel +	23	94	17	94

Study	Intervention	Comparison	Intervention		Comparison	
			Events	n	Events	n
		aspirin				
Montalescot 2009 (TRITON)[18]	Prasugrel + aspirin	Clopidogrel + aspirin	35	1769	57	1765
Alexopoulos 2012[1]	Prasugrel + aspirin	Ticagrelor + aspirin	1	27	3	28
Motovska 2016 (PRAGUE18)[19]	Prasugrel + aspirin	Ticagrelor + aspirin	24	634	22	596
Parodi 2013 (RAPID I)[21]	Prasugrel + aspirin	Ticagrelor + aspirin	0	25	3	25
Parodi 2014 (RAPID II)[20]	Prasugrel + aspirin	Ticagrelor + aspirin	0	25	2	25

n = number of participants

3.5.2 Results of network meta-analysis

Table 25 summarises the results of the pairwise meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA (this is from a fixed effects model, which was chosen on the basis of model fit (see section 3.5.3)) in terms of risk ratios for every possible treatment comparison. Table 26 presents summary statistics for the three interventions included in the network, including the rank of the intervention, probability of the intervention being the best and mean probability of an event.

Table 25: Risk ratios for minor bleeding at 30 days; direct pairwise meta-analysis results and NMA results

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

Table 26: Intervention ranks and mean probability of event – minor bleeding [results are based on baseline results informed by the estimate of TRITON from a fixed effect model]

	Probability of minor bleeding by day 30 - posterior mean (95% credible intervals) and per 1000 patients	Intervention rank – median (95% CrIs)	Probability intervention is best (%)
Clopidogrel + aspirin	0.0323 (0.0248, 0.0414) 32 per 1000 patients	2 (1,3)	4%
Ticagrelor + aspirin	0.0410 (0.0259, 0.0613)	3 (2,3)	0%

	Probability of minor bleeding by day 30 - posterior mean (95% credible intervals) and per 1000 patients	Intervention rank – median (95% CrIs)	Probability intervention is best (%)
	41 per 1000 patients		
Prasugrel + aspirin	0.0241 (0.0152, 0.0363) 24 per 1000 patients	1 (1,2)	96%

3.5.3 Inconsistency and goodness of fit

As only one study informed the baseline model, only the fixed effects baseline model was fitted to the data from the TRITON trial. The fixed effects baseline was used to combine with the relative effects from the NMA to obtain absolute probabilities and relative risks outputs

There was no evidence of heterogeneity in the NMA, as there were no meaningful differences in terms of the fit and DIC between the fixed and random effects NMA models. The simpler, fixed effects model was therefore preferred.

An inconsistency model was run and the model fit statistics were as seen in Table 21. There are no meaningful differences between the fit and DIC of the NMA and inconsistency models,suggesting that there is no evidence of inconsistency, a conclusion which is supported by comparing risk ratios from the pairwise and NMA models (Table 25).

* Note only 1 study informing the baseline model, therefore random effects model is not applicable.
    (a) Number of data points in baseline model (n=2)
    (b) Number of data points in the NMA and inconsistency models (n=20)

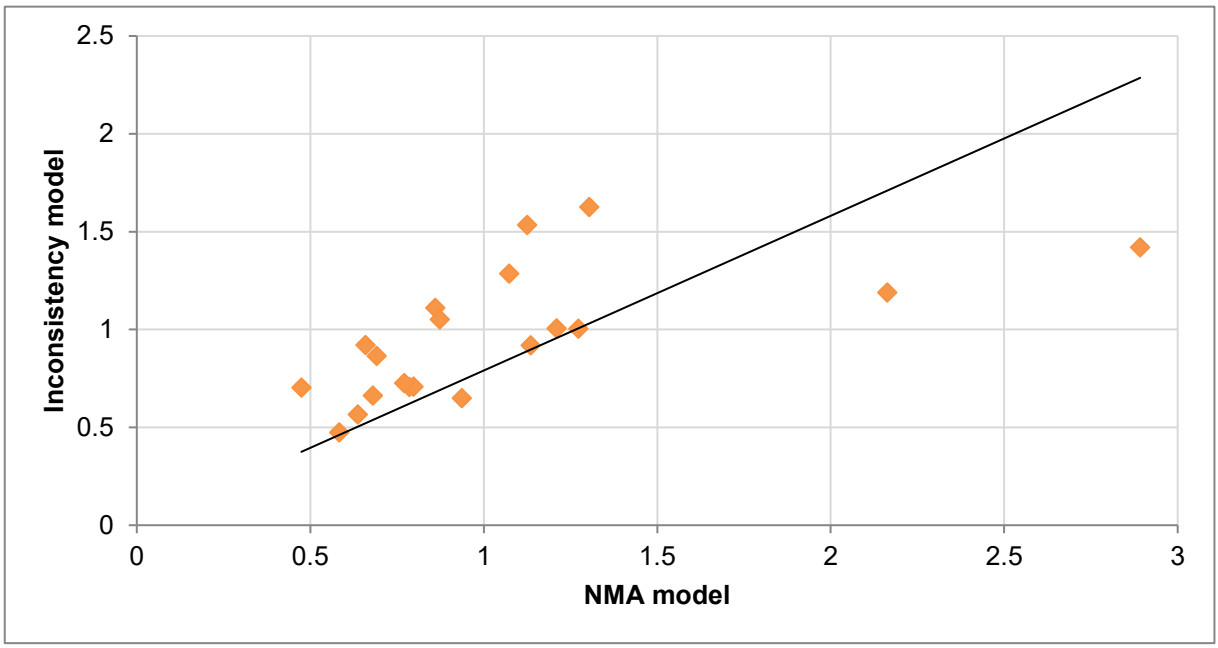
Figure 10 presents the contributions to the posterior mean of the deviances for each data-point for the inconsistency model against that for the consistency NMA model. The posterior mean of the deviances of the inconsistency model shows there are some data points better predicted by the inconsistency model (below the line of equality), demonstrating some evidence of inconsistency. Motovska 2016 (PRAGUE18)[19] was notably better predicted by the inconsistency model, and this study compared treatments ticagrelor in combination with aspirin and prasugrel in combination with aspirin.

Table 27: Model fit statistics – minor bleeding

	Deviance information criterion (DIC)	Mean of the residual deviance (ResDev)
Baseline models		
Fixed effects	7.86	1.0
Random effects*	-	-
Relative effect models		
NMA Fixed effects	105.85	20.9
NMA Random effects	106.27	18.4
Inconsistency model [FE]	105.02	19.1

* Note only 1 study informing the baseline model, therefore random effects model is not applicable.
    (c) Number of data points in baseline model (n=2)
    (d) Number of data points in the NMA and inconsistency models (n=20)

Figure 10: Posterior mean of the contribution to the posterior mean residual deviance of the inconsistency model vs. the consistency model – minor bleeding



4 Risk of bias

There currently is not an established method for assessing risk of bias in a NMA, however the risk of bias assessment conducted for the outcomes included in pairwise meta-analysis can provide an overall assessment.

As seen in Table 28, the majority of the relevant evidence for the NMAs had a low risk of bias. For studies were there was high or very high risk of bias, this was due to concerns about selection bias. Full risk of bias details can be found in the evidence review for dual antiplatelet therapy.

Table 28: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome

Study	All-cause mortality	New myocardial infarction	Stroke	Major bleeding	Minor bleeding
Dehghani 2017[8]	Low RoB	Low RoB	-	Low RoB	Low RoB
Cannon 2007 (DISPERSE-2)[6]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB
Wallentin 2009 (PLATO)[27]	High RoB	High RoB	High RoB	High RoB	-
Roe 2012 (TRILOGY)[22]	Low RoB	Low RoB	Low RoB	Low RoB	-
Zeymer 2015 (ETAMI)[30]	Low RoB	-	-	-	-
Montalescot 2009 (TRITON)[18]	High RoB	High RoB	High RoB	High RoB	High RoB
Alexopoulos 2012[1]	Low RoB	-	-	-	Low RoB
Motovska 2016 (PRAGUE18)[19]	Low RoB	Low RoB	Low RoB	Low RoB	Low RoB
Parodi 2013 (RAPID I)[21]	Low RoB	Low RoB			Low RoB
Parodi 2014 (RAPID II)[20]	Low RoB	-	-	Low RoB	Low RoB
Wang 2016b[28]	-	High RoB	High RoB	-	-
Wang 2019[29]	High RoB	High RoB	-	High RoB	High RoB
Han 2019[12]	-	High RoB	-	-	High RoB
Bonello 2015[2]	-	-	Low RoB	Low RoB	-
Jing 2016[13]	High RoB	-	-	-	High RoB
Dasbiswas 2013[7]	High RoB	-	High RoB	-	-
Laine 2014[14]	Low RoB	Low RoB	-	-	-

4.1 Sensitivity analysis for risk of bias

A sensitivity analysis was run for all outcomes, where studies at high risk of bias were removed from the NMA. We re-ran the NMA model on the data provided by the low risk of bias studies and compared the resulting estimated relative risks to those estimated in the NMA of all studies, as seen in Figure 11, Figure 12, Figure 13, Figure 14 and Figure 15.

Figure 11: Relative effects for comparisons, all studies versus low risk of bias studies – all-cause mortality

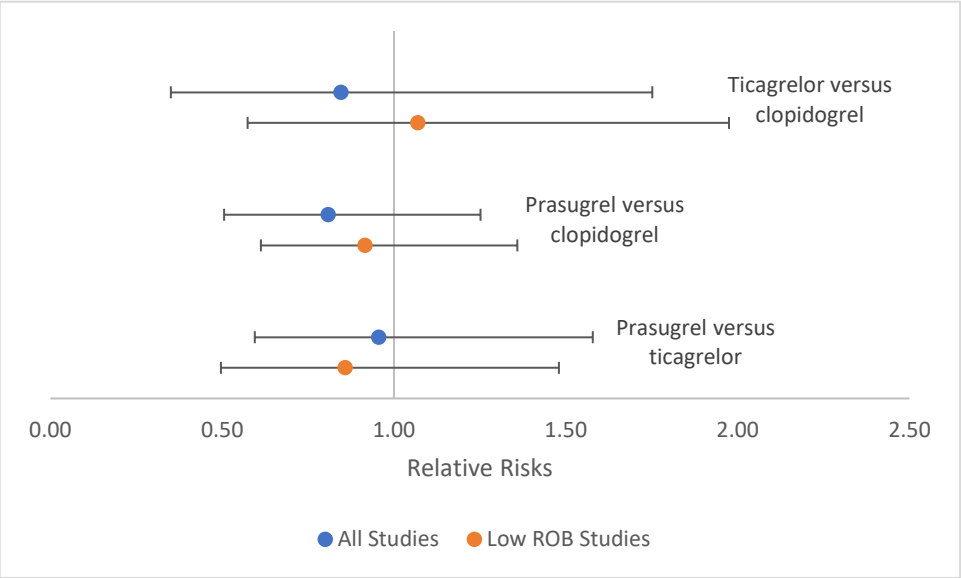


Figure 12: Relative effects for comparisons, all studies versus low risk of bias studies – new MI

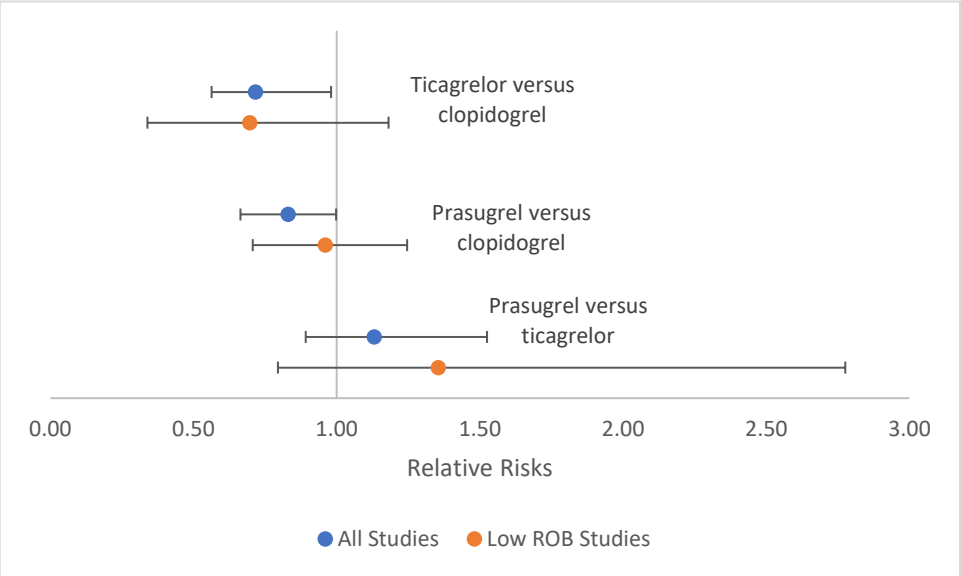


Figure 13: Relative effects for comparisons, all studies versus low risk of bias studies – stroke

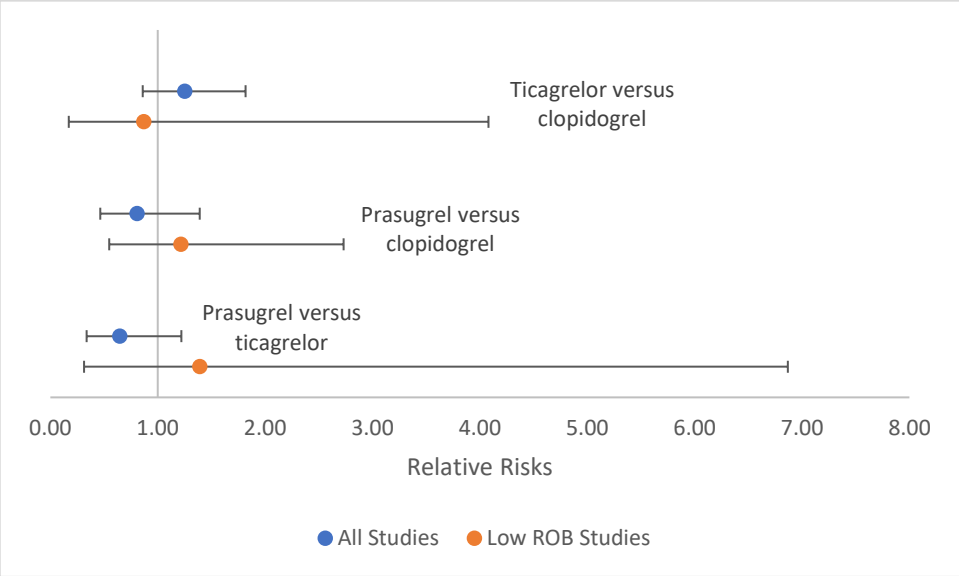


Figure 14: Relative effects for comparisons, all studies versus low risk of bias studies – major bleeding

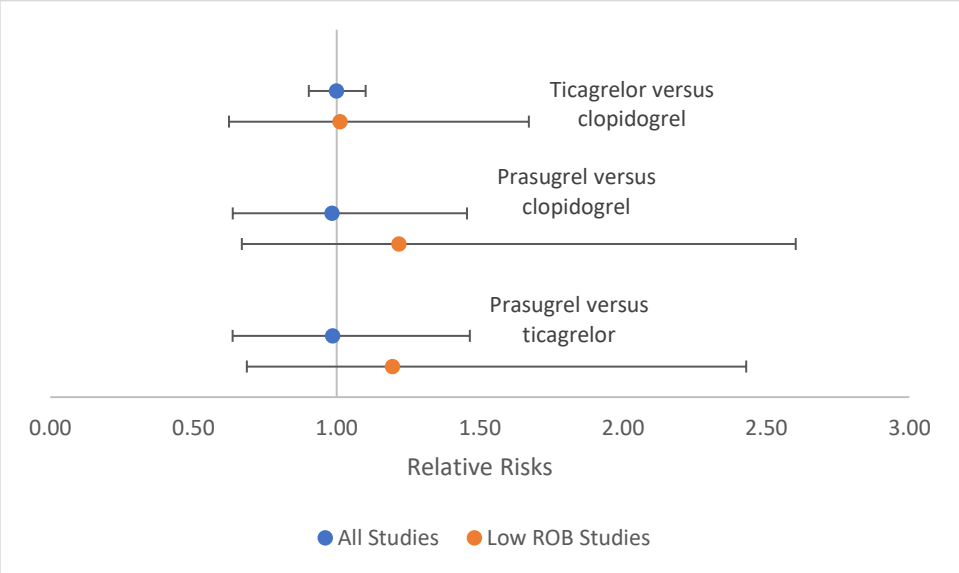
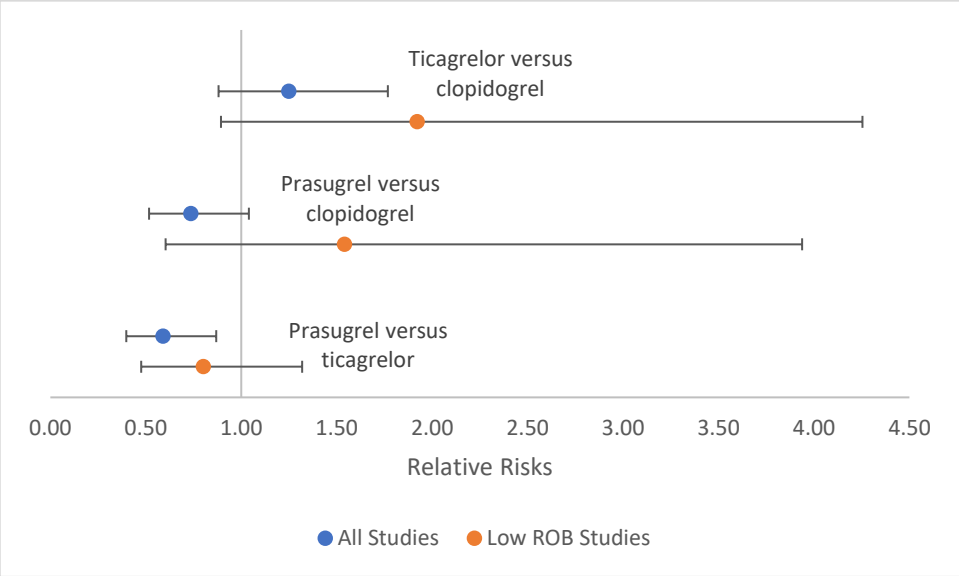


Figure 15: Relative effects for comparisons, all studies versus low risk of bias studies – minor bleeding



We note that for some comparisons, the estimates based on the low risk of bias studies suggested a different direction of effect, although there is wide uncertainty in the estimates. These differences are evident in the relative risks reported in Table 29.

Table 29: Comparisons with differing relative risks – main analysis with all studies versus sensitivity analysis

	Intervention vs comparison	Relative risk – median (95% credible intervals	
		All studies	Low risk of bias studies
All-cause mortality	Ticagrelor versus clopidogrel	0.85 (0.70, 1.02)	1.07 (0.57, 1.98)
Stroke	Ticagrelor versus clopidogrel	1.25 (0.86, 1.82)	0.87 (0.17, 4.08)
	Prasugrel versus clopidogrel	0.81 (0.47, 1.39)	1.22 (0.55, 2.73)
	Prasugrel versus ticagrelor	0.65 (0.34, 1.22)	1.39 (0.31, 6.87)
Major bleeding	Ticagrelor versus clopidogrel	1.00 (0.90, 1.10)	1.01 (0.62, 1.67)
	Prasugrel versus clopidogrel	0.98 (0.64, 1.46)	1.22 (0.67, 2.60)
	Prasugrel versus ticagrelor	0.99 (0.64, 1.47)	1.20 (0.69, 2.43)
Minor bleeding	Prasugrel versus ticagrelor	0.59 (0.40, 0.87)	0.80 (0.48, 1.32)

5 Evidence statements

All-cause mortality at 30 days

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

New MI at 30 days

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

Stroke at 30 days

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

Major bleeding at 30 days

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

Minor bleeding at 30 days

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

6 Discussion

NMAs were conducted for five outcomes (all-cause mortality, new MI, stroke, major bleeding and minor bleeding). Three dual anti-platelet interventions were included in all of the networks. The NMA findings have increased the robustness of the conventional pairwise meta-analysis summary statistics reported in the evidence review for dual antiplatelet therapy. These results were used to inform committee decision-making when making recommendations.

For the all-cause mortality network, fourteen studies were included. There is some evidence suggesting both prasugrel in combination with aspirin and ticagrelor in combination with aspirin may both be more effective than clopidogrel in combination with aspirin in reducing the risk of mortality, although this isn't conclusive. There is no evidence to suggest a difference between the effectiveness of prasugrel in combination with aspirin and ticagrelor in combination with aspirin.

For the new MI network, eleven studies were included. The evidence shows ticagrelor in combination with aspirin may be more effective than clopidogrel in combination with aspirin in reducing the risk of MI. There is also some evidence suggesting prasugrel in combination with aspirin may be more effective than clopidogrel in combination with aspirin in reducing the risk of MI, although this isn't conclusive. There is no evidence to suggest a difference between the effectiveness of prasugrel in combination with aspirin and ticagrelor in combination with aspirin.

For the stroke network, eight studies were included. The evidence suggests that prasugrel in combination with aspirin may be more effective than clopidogrel in combination with aspirin and ticagrelor in combination with aspirin in reducing the risk of stroke. Clopidogrel in combination with aspirin may also be more effective ticagrelor in combination with aspirin, althought this isn't conclusive. There were similar findings (relative effects and level of uncertainty) for the minor bleeding network which included ten studies.

For the major bleeding network, ten studies were included. There is no evidence to suggest a difference in the effectiveness between the three treatments in terms of reducing the risk of major bleeding.

In summary, all five networks seemed to fit well, with the exception of minor bleeding. However due to the low event rates, the credible intervals around the relative risks for the interventions in all the networks were wide suggesting considerable uncertainty about these results (particularly for stroke, major bleeding and minor bleeding network). These results need to be interpreted alongside the one-year trial results and considered as part of a cost effectiveness analysis.

7 Conclusions

These network meta-analyses enabled us to combine estimates for the three interventions: ticagrelor in combination with aspirin, prasugrel in combination with aspirin and clopidogrel in combination with aspirin. The committee reviewed the results for the five critical outcomes and noted that the evidence suggests that prasugrel in combination with aspirin and ticagrelor in combination with aspirin may be more clinically effective than clopidogrel in combination with aspirin for most of the outcomes. There was however particularly less certainty around the difference in effectiveness between prasugrel and ticagrelor and overall notably uncertainty in the networks with overlapping credible intervals.

These results informed a health economic model that was developed for this review question. For details of the health economic model and results, please refer to the Health Economic Analysis document for the dual antiplatelet therapy review, .

For details of the rationale and discussion leading to recommendations, please refer to the section linking the evidence to the recommendations (section 1.8, evidence review on dual anti-platelet therapy).

References

1. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circulation: Cardiovascular Interventions. 2012; 5(6):797-804

2. Bonello L, Laine M, Cluzel M, Frere C, Mancini J, Hasan A et al. Comparison of ticagrelor versus prasugrel to prevent periprocedural myonecrosis in acute coronary syndromes. American Journal of Cardiology. 2015; 116(3):339-343

3. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. Journal of Computational and Graphical Statistics. 1998; 7(4):434-455

4. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of Clinical Epidemiology. 1997; 50(6):683-91

5. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ. 2005; 331(7521):897-900

6. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: Primary results of the DISPERSE-2 trial. Journal of the American College of Cardiology. 2007; 50(19):1844-1851

7. Dasbiswas A, Rao MS, Babu PR, Vijayvergiya R, Nayak R, Dani S et al. A comparative evaluation of prasugrel and clopidogrel in patients with acute coronary syndrome undergoing percutaneous coronary intervention. Journal of the Association of Physicians of India. 2013; 61(2):114-6, 126

8. Dehghani P, Lavoie A, Lavi S, Crawford JJ, Harenberg S, Zimmermann RH et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. American Heart Journal. 2017; 192:105-112

9. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making. 2013; 33(5):607-617

10. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making. 2013; 33(5):641-656

11. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Statistical Science. 1992; 7(4):457-472

12. Han L, Zhang JJ, Jing HF, Qin L. Ticagrelor for patients with ST-segment elevation myocardial infarction after emergency percutaneous coronary intervention. Journal of Biological Regulators and Homeostatic Agents. 2019; 33(2):485-490

13. Jing R, Lin W. Comparison of ticagrelor with clopidogrel in Chinse ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. International Journal of Clinical and Experimental Medicine. 2016; 9(12):23525-23529

14. Laine M, Frère C, Toesca R, Berbis J, Barnay P, Pansieri M et al. Ticagrelor versus prasugrel in diabetic patients with an acute coronary syndrome. A pharmacodynamic randomised study. Thrombosis and Haemostasis. 2014; 111(2):273-278

15. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine. 2004; 23(20):3105-24

16. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. The BUGS Book – a practical introduction to Bayesian analysis. Boca Raton. CRC Press. 2012.

17. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS - A Bayesian modelling framework: Concepts, structure, and extensibility. Statistics and Computing. 2000; 10(4):325-337

18. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. Lancet. 2009; 373(9665):723-731

19. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: Multicenter randomized PRAGUE-18 Study. Circulation. 2016; 134(21):1603-1612

20. Parodi G, Bellandi B, Valenti R, Migliorini A, Marcucci R, Carrabba N et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. American Heart Journal. 2014; 167(6):909-914

21. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. Journal of the American College of Cardiology. 2013; 61(15):1601-1606

22. Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. New England Journal of Medicine. 2012; 367(14):1297-1309

23. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. New England Journal of Medicine. 2019; 381:1524-1534

24. Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society: Series B (Statistical Methodology). 2002; 64(4):583-639

25. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statistics in Medicine. 2004; 23(9):1351-1375

26. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Research Synthesis Methods. 2016; 7(1):80-93

27. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine. 2009; 361(11):1045-1057

28. Wang H, Wang X. Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patients with acute coronary syndrome. Therapeutics and Clinical Risk Management. 2016; 12:1101-1105

29. Wang X, Li X, Wu H, Li R, Liu H, Wang L et al. Beneficial effect of ticagrelor on microvascular perfusion in patients with ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention. Coronary Artery Disease. 2019; 30(5):317-322

30. Zeymer U, Mochmann HC, Mark B, Arntz HR, Thiele H, Diller F et al. Double-blind, randomized, prospective comparison of loading doses of 600 mg clopidogrel versus 60 mg prasugrel in patients with acute ST-segment elevation myocardial infarction scheduled for primary percutaneous intervention: The ETAMI trial (early thienopyridine treatment to improve primary PCI in patients with acute myocardial infarction). JACC: Cardiovascular Interventions. 2015; 8(1 Pt B):147-154

Appendices

Appendix A: WinBUGS Code

A.1 Relative effects code (example of all-cause mortality at 30 days provided)

A.1.1 Random effects

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
```

```
        sw[i,k] <- sum(w[i,1:k-1])/(k-1)
      }
  }
totresdev <- sum(resdev[])          # Total Residual Deviance
d[1]<-0       # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

rr[1]<- 1
for (k in 2:nt)  {
rr[k]<- T[k]/T[1]  }                        # calculate relative risk


# Ranking and prob{treatment k is best}
 for (k in 1:nt) {
            rk[k]<-rank(rr[],k)
best[k]<-equals(rank(rr[],k),1)}

# pairwise ORs and RRs
for (c in 1:(nt-1))
        {  for (k in (c+1):nt)
             {  lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                lrr[c,k] <- log(rr[k]) - log(rr[c])
                log(rrisk[c,k]) <- lrr[c,k]

```

```
            }
        }
}

}                           # *** PROGRAM ENDS

 Data
# ns= number of studies; nt=number of treatments
list(ns=9, nt=3, meanA=-3.73, precA=249.57)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 3 68 1 76 NA NA NA NA NA NA 1 2 NA NA NA 2
 2 327 9 663 NA NA NA NA NA NA 1 2 NA NA NA 2
 212 9186 179 9235 NA NA NA NA NA NA 1 2 NA NA NA 2
 44 4663 39 4663 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 31 1 31 NA NA NA NA NA NA 1 3 NA NA NA 2
 45 1765 28 1769 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 28 3 27 NA NA NA NA NA NA 2 3 NA NA NA 2
 16 596 14 634 NA NA NA NA NA NA 2 3 NA NA NA 2
 1 25 1 25 NA NA NA NA NA NA 2 3 NA NA NA 2

END

Initial Values
#chain 1
list(d=c( NA,1,-1), sd=1, mu=c(0, 1, 2, 0,-1, 3, 0, 0, 1))

#chain 2
list(d=c( NA, 0, 2), sd=4, mu=c(-3, 0, 1, 0, 2, -1, 0, 1, 0))

#chain 3
list(d=c( NA, 3, 0), sd=2, mu=c(0, 0, -1, -3, 1, 1, -2, 0, 2))
```

A.1.112 Fixed effects

```
# Binomial likelihood, logit link
# Fixed effects model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)     # vague priors for all trial baselines
   for (k in 1:na[i])  {      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
    }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }

rr[1]<- 1
for (k in 2:nt)  {
rr[k]<- T[k]/T[1]  }                    # calculate relative risk

```

```
1
2   # Ranking and prob{treatment k is best}
3    for (k in 1:nt) {
4                rk[k]<-rank(rr[],k)
5   best[k]<-equals(rank(rr[],k),1)}
6
7   # pairwise ORs and RRs
8   for (c in 1:(nt-1))
9           {  for (k in (c+1):nt)
10               {  lor[c,k] <- d[k] - d[c]
11                  log(or[c,k]) <- lor[c,k]
12                  lrr[c,k] <- log(rr[k]) - log(rr[c])
13                  log(rrisk[c,k]) <- lrr[c,k]
14
15               }
16           }
17  }
18
19  }                                       # *** PROGRAM ENDS
20
21
22   Data
23  # ns= number of studies; nt=number of treatments
24  # Results from FE baseline model (2 studies)
25  list(ns=9, nt=3, meanA=-3.73, precA=249.57)
26
27   r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]     na[]
28   3 68 1 76 NA NA NA NA NA NA 1 2 NA NA NA 2
29   2 327 9 663 NA NA NA NA NA NA 1 2 NA NA NA 2
30   212 9186 179 9235 NA NA NA NA NA NA 1 2 NA NA NA 2
31   44 4663 39 4663 NA NA NA NA NA NA 1 3 NA NA NA 2
32   1 31 1 31 NA NA NA NA NA NA 1 3 NA NA NA 2
33   45 1765 28 1769 NA NA NA NA NA NA 1 3 NA NA NA 2
```

```
 1 28 3 27 NA NA NA NA NA NA 2 3 NA NA NA 2
 16 596 14 634 NA NA NA NA NA NA 2 3 NA NA NA 2
 1 25 1 25 NA NA NA NA NA NA 2 3 NA NA NA 2

END


 Initial Values
list(d=c( NA, 0,0), mu=c(0, 0, 0, 1, 0, 1, 0, 2, 0))
#chain 2
list(d=c( NA, -1,-1), mu=c(3, 0, -3, -1, 0, -2, 0, 1, 1))
#chain 3
list(d=c( NA, 2,0), mu=c(-3, 2, -1, -2, 0, 0, -1, -3, 0))
```

A.1.2 Baseline model

A.1.2.1 Random effects

```
# Binomial likelihood, logit link
# Baseline random effects model
model{                    # *** PROGRAM STARTS
for (i in 1:ns){          # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])              # Likelihood
   logit(p[i]) <- mu[i]                          # Log-odds of response
                  mu[i] ~ dnorm(m,tau.m)     # Random effects model

                  # expected value of the numerators
   rhat[i] <- p[i] * n[i]
                  #Deviance contribution
   dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
         +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
  }
totresdev <- sum(dev[])                                  # total residual deviance

```

```
mu.new ~ dnorm(m,tau.m)          # predictive dist. (log-odds)
m ~ dnorm(0,.0001)               # vague prior for mean
var.m <- 1/tau.m                 # between-trial variance
tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)
sd.m ~ dunif(0,5)                # vague prior for between-trial SD
#tau.m ~ dgamma(0.001,0.001)
#sd.m <- sqrt(var.m)
logit(R) <- m                    # posterior probability of response
logit(R.new) <- mu.new           # predictive probability of response
}
```

Data

```
list(ns=2)  # ns=number of studies

r[]        n[]
212      9186
45    1765
END
```

Inits

```
list(mu=c(0, 2), sd.m=1, m=0)

list(mu = c(-1, 0), sd.m=2, m= -1)

list(mu = c(0, 0), sd.m = 0.5, m = 1)
```

A.1.2.2 Fixed effects

```
# Binomial likelihood, logit link
# Baseline fixed effect model
model{                    # *** PROGRAM STARTS
```

```
for (i in 1:ns){              # LOOP THROUGH STUDIES
   r[i] ~ dbin(p[i],n[i])              # Likelihood
   logit(p[i]) <- m                                    # Log-odds of response

                  # expected value of the numerators
   rhat[i] <- p[i] * n[i]
                  #Deviance contribution
   dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
         +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
  }
totresdev <- sum(dev[])                              # total residual deviance
m ~ dnorm(0,.0001)            # vague prior for mean
logit(R) <- m                 # posterior probability of response
}
```

Data

```
list(ns=2)  # ns=number of studies

r[]       n[]      #        Study ID
212     9186   #        1
45   1765      #    2
END
```

Inits

```
list(m=0)

list(m= -1)

list(m = 1)
```

A.1.3 Fixed effects inconsistency model

```
# Binomial likelihood, logit link
# Fixed effects INCONSISTENCY model
model{                    # *** PROGRAM STARTS
for(i in 1:ns){           # LOOP THROUGH STUDIES
   mu[i] ~ dnorm(0,.0001)     # vague priors for all trial baselines
   for (k in 1:na[i])  {      # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
      logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]
# expected value of the numerators
      rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
    }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
    }
totresdev <- sum(resdev[])     # Total Residual Deviance

# vague priors for treatment effects
for (c in 1:(nt-1)){
                  d[c,c]<-0
     for (k in (c+1):nt){
        d[c,k] ~ dnorm(0,.0001)                    # priors for all mean trt effects
```

```
            or[c,k] <- exp(d[c,k])                    # all pairwise ORs
        }
                    }

}                                   # *** PROGRAM ENDS
 Data
# ns= number of studies; nt=number of treatments
list(ns=9, nt=3)

 r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1]  t[,2]  t[,3]     t[,4]     t[,5]    na[]
 3 68 1 76 NA NA NA NA NA NA 1 2 NA NA NA 2
 2 327 9 663 NA NA NA NA NA NA 1 2 NA NA NA 2
 212 9186 179 9235 NA NA NA NA NA NA 1 2 NA NA NA 2
 44 4663 39 4663 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 31 1 31 NA NA NA NA NA NA 1 3 NA NA NA 2
 45 1765 28 1769 NA NA NA NA NA NA 1 3 NA NA NA 2
 1 28 3 27 NA NA NA NA NA NA 2 3 NA NA NA 2
 16 596 14 634 NA NA NA NA NA NA 2 3 NA NA NA 2
 1 25 1 25 NA NA NA NA NA NA 2 3 NA NA NA 2
END

 Initial Values

list(mu=c(0, 0, 0, 1, 0, 1, 0, 2, 0),
d=structure(.Data=c(NA,0,0,   NA,NA,0), .Dim=c(2,3))
)
```

```
1
2   #chain 2
3   list(mu=c(3, 0, -3, -1, 0, -2, 0, 1, 1),
4   d=structure(.Data=c(NA,-1,-1,   NA,NA,-1), .Dim=c(2,3))
5   )
6
7   #chain 3
8   list(mu=c(-3, 2, -1, -2, 0, 0, -1, -3, 0),
9   d=structure(.Data=c(NA,2,0.5,   NA,NA,1), .Dim=c(2,3))
10  )
11
```

Appendix B: Bucher test for inconsistency

Table 30: Results from the Bucher test for inconsistency[4] for 1 year outcomes

	Intervention comparison	OR point estimate	OR LCI	OR UCI	LOR	Var LOR	Omega	Var Omega	Z statistic	p-value
All-cause mortality										
B vs C	Prasugrel vs clopidogrel	1.00	0.83	1.21	0	0.009459				
A vs C	Ticagrelor vs clopidogrel	0.77	0.68	0.88	-0.26136	0.004642				
A vs B	Ticagrelor vs prasugrel	1.24	0.90	1.70	0.215111	0.025915				
B vs C (indirect)	*Prasugrel vs clopidogrel*	*0.62*	*0.44*	*0.87*	*-0.47648*	*0.030556*	*0.476*	*0.040*	*2.382*	*0.017*
Reinfarction										
B vs C	Prasugrel vs clopidogrel	0.75	0.66	0.84	-0.28768	0.003343				
A vs C	Ticagrelor vs clopidogrel	0.82	0.73	0.92	-0.19845	0.003447				
A vs B	Ticagrelor vs prasugrel	1.63	1.17	2.26	0.48858	0.027799				
B vs C (indirect)	*Prasugrel vs clopidogrel*	*0.50*	*0.36*	*0.71*	*-0.68703*	*0.031246*	*0.399*	*0.035*	*2.147*	*0.032*
Stroke										
B vs C	Prasugrel vs clopidogrel	0.93	0.67	1.30	-0.07257	0.029203				
A vs C	Ticagrelor vs clopidogrel	1.13	0.89	1.44	0.122218	0.015299				
A vs B	Ticagrelor vs prasugrel	1.16	0.62	2.14	0.14842	0.097623				
B vs C	*Prasugrel vs*	*0.97*	*0.50*	*1.88*	*-0.0262*	*0.112922*	*0.046*	*0.142*	*0.123*	*0.902*

	Intervention comparison	OR point estimate	OR LCI	OR UCI	LOR	Var LOR	Omega	Var Omega	Z statistic	p-value
(indirect)	*clopidogrel*									
Major bleeding										
B vs C	Prasugrel vs clopidogrel	1.43	1.14	1.79	0.357674	0.013125				
A vs C	Ticagrelor vs clopidogrel	1.04	0.95	1.14	0.039221	0.002194				
A vs B	Ticagrelor vs prasugrel	1.06	0.78	1.44	0.058269	0.024435				
B vs C (indirect)	*Prasugrel vs clopidogrel*	*0.98*	*0.71*	*1.35*	*-0.01905*	*0.026629*	*0.377*	*0.040*	*1.889*	*0.059*

(a) Abbreviations: LOR = log odds ratio; OR = odds ratio; Var = variance

Appendix C: Odds ratios

Table 31 shows the odds ratios obtained from the NMA that were used in the cost effectiveness analysis. Further details on this analysis can be found in the PDF file 'Health Economic Analysis_DAPT'.

Table 31: Odds ratios for outcomes at 30 days from NMA results

Outcomes	Intervention	Odds ratio (95% confidence interval) versus clopidogrel
All-cause mortality	Ticagrelor	0.84 (0.69 to1.02)
	Prasugrel	0.82 (0.64 to 1.03)
New myocardial infarction	Ticagrelor	0.69 (0.55 to 0.85)
	Prasugrel	0.79 (0.64 to 0.97)
Stroke	Ticagrelor	1.28 (0.86 to 1.83)
	Prasugrel	0.83 (0.45 to 1.39)
Major bleed	Ticagrelor	1.00 (0.89 to 1.11)
	Prasugrel	0.99 (0.61 to 1.52)
Minor bleed	Ticagrelor	1.18 (0.75 to 1.78)
	Prasugrel	0.74 (0.50 to 1.05)