Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
HTA report 2021:123

Clopidogrel versus ticagrelor as part of dual antiplatelet therapy for patients with acute coronary syndrome

Myredal A, Bergh N, Liljegren A, Nivedahl P, Petzold M, Sjövall H, Stadig I, Svensson M, Wartenberg C, Zarin S, Wallerstedt SM

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Clopidogrel versus ticagrelor as part of dual antiplatelet therapy for patients with acute coronary syndrome

[Klopidogrel vid dubbel trombocythämning jämfört med tikagrelor för patienter som vårdats för akut koronart syndrom]

Myredal A[1*], Bergh N[1,2], Liljegren A[3], Nivedahl P[1], Petzold M, Sjövall H[4], Stadig I[3], Svensson M[4], Wartenberg C[4], Zarin S[5], Wallerstedt SM[4]

[1] Region Västra Götaland, Department of Cardiology, Sahlgrenska University hospital, Gothenburg, Sweden
[2] Region Västra Götaland, Department of Molecular and Clinical Medicine/Wallenberg Laboratory, University of Gothenburg, Gothenburg, Sweden
[3] Region Västra Götaland, Medical Library, Sahlgrenska University Hospital, Gothenburg, Sweden
[4] Region Västra Götaland, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
[5] Region Västra Götaland, Department of Cardiology, Kungälv Hospital, Kungälv, Sweden

[*]Corresponding author

Published May 2021
2021:123
Suggested citation: Myredal A, Bergh N, Liljegren A, Nivedahl P, Sjövall H, Stadig I, Svensson M, Wartenberg C, Zarin S, Wallerstedt SM.[Klopidogrel jämfört med tikagrelor för patienter som vårdats för akut koronart syndrom] Clopidogrel versus ticagrelor as part of dual antiplatelet therapy for patients with acute coronary syndrome. Göteborg: Västra Götalandsregionen, Sahlgrenska Universitetssjukhuset, HTA-centrum: 2021.
Regional activity-based HTA 2021:123

Table of contents

1. Abstract

Background To prevent further cardiovascular (CV) events after acute coronary syndrome (ACS), including myocardial infarction (MI) with or without ST-segment elevation as well as unstable angina pectoris, dual antiplatelet therapy (DAPT) is usually prescribed for 12 months, mainly ticagrelor or clopidogrel, each combined with acetylsalicylic acid (ASA). Based on a large double-blind randomised controlled trial (RCT, acronym: PLATO), published in 2009 and showing that ticagrelor was superior to clopidogrel regarding the primary composite endpoint of vascular death, non-fatal myocardial infarction (MI) and stroke without inducing an increased risk of major bleeding, the European Society of Cardiology recommends ticagrelor and ASA as the first-line DAPT treatment. In 2019, more than 80% of the 2,758 ACS patients in Region Västra Götaland were treated with ticagrelor, the remaining 20% primarily being patients treated with clopidogrel because of concomitant treatment with a direct-acting oral anticoagulant or warfarin. However, improvements in revascularisation techniques make it uncertain to what extent the PLATO results are applicable in current clinical practice. For instance, percutaneous coronary intervention (PCI) techniques have improved, with a reduced risk of thrombotic events. Further, the increased age in the population at issue for DAPT may affect the risk of adverse events as the risk of bleeding increases by age.

Question at issue In ACS patients subjected to DAPT, including those of older age, is clopidogrel combined with ASA similar to ticagrelor combined with ASA, regarding the outcomes mortality, MI, bleeding, stent thrombosis, angina, rehospitalisation, health-related quality of life (HRQL), and dyspnea?

Methods Two authors performed searches (September 2019, updated in September 2020) in PubMed, Embase, the Cochrane Library, Medline and a number of health technology assessment (HTA) databases. They independently assessed the abstracts, and selected, in consensus, full-text articles to be sent to the other authors, who then decided in consensus on inclusion/exclusion. The included studies were critically appraised, and data were extracted. Certainty of evidence was assessed according to GRADE.

Results Out of 3,102 unique studies identified in the search, 35 RCTs including 31,389 patients and 46 non-RCTs including 545,537 patients provided data regarding ACS patients subjected to DAPT. Two RCTs including 1,202 patients and two non-RCTs including 14,481 patients provided data regarding older ACS patients subjected to DAPT. As the handling of zero-event RCTs in meta-analyses is disputable, absolute risk differences (RD), i.e. clopidogrel minus ticagrelor, are presented with and without these trials for outcomes where the meta-analysis methods showed discordant results (with 95% confidence interval in parenthesis). When the results were concordant, meta-analysis results including zero-event trials are presented.

The outcomes ***all-cause mortality, HRQL and rehospitalisation*** reflect the net effect of drug treatment, i.e. benefits and risks combined (benefit-risk balance). ***In all ACS patients***, for ***all-cause mortality*** with rates ranging between 0% and 9% in the ticagrelor group, the pooled RDs with and without zero-event trials were 0.7% (0.2% to 1.2%) and 0.5% (-0.3% to 1.4%), respectively. For ***HRQL*** and ***rehospitalisations***, all RCTs had major study limitations and data were too uncertain for conclusions. ***In older ACS patients***, there was no significant difference in all-cause mortality, and no studies provided results regarding HRQL or rehospitalisation.

Conclusions: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may be slightly less efficient in reducing the risk of all-cause mortality but shows little or no difference when zero-event trials are excluded (GRADE ⊕⊕◯◯), and it is uncertain whether HRQL or rehospitalisation rates are affected (GRADE ⊕◯◯◯).

In *older* ACS patients, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of all-cause mortality (GRADE ⊕⊕◯◯).

The outcomes ***CV mortality, MI, stent thrombosis and angina*** reflect the intended benefits of DAPT. ***In all ACS patients***, for ***CV mortality*** with rates ranging between 0% and 6% in the ticagrelor group,

the pooled RDs with and without zero-event trials were 0.6% (0.2% to 1.0%) and 0.4% (-0.3% to 1.1%), respectively. For ***MI***, with rates ranging between 0% and 7.4% in the ticagrelor group, the pooled RD was 0.8% (0.4% to 1.3%), and for ***stent thrombosis***, with rates ranging between 0% and 1.3%, the pooled RD was 0.7% (0.4% to 1.1%). For ***angina***, all studies had major problems, the event rate ranging between 0% and 8% in the ticagrelor group, and the pooled RD was 6.5% (2.9% to 10%). ***In older ACS patients***, there was no significant difference for the outcomes CV mortality, and MI. For stent thrombosis, the results were inconclusive for older patients, and no studies provided results regarding angina.

> *Conclusions:* In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor is probably slightly less efficient in reducing the risk of MI (GRADE ⊕⊕⊕◯) and stent thrombosis (GRADE ⊕⊕⊕◯). Clopidogrel may be less efficient in reducing the risk of angina (GRADE ⊕⊕◯◯). Clopidogrel may be slightly less efficient in reducing the risk of CV mortality but shows little or no difference when zero-event trials are excluded (GRADE ⊕⊕◯◯).
>
> In older ACS patients, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of CV mortality and MI (GRADE ⊕⊕◯◯), and it is uncertain whether the risk of stent thrombosis is affected (GRADE ⊕◯◯◯).

Bleedings and dyspnea are adverse events reflecting the risks of the drug treatment. ***In all ACS patients***, for ***clinically significant bleeding*** defined as major bleedings and bleedings requiring surgical or medical intervention and rates ranging between 0% and 24% in the ticagrelor group, the pooled absolute RD was -1.9% (-3.6% to -0.2%). For all double- and single-blind RCTs, the rate of clinically significant bleeding was higher in the ticagrelor group. For ***major bleeding***, the rate ranged between 0% and 10%, and the pooled RDs with and without zero-event trials were -0.2% (-0.6% to 0.2%) and -0.8% (-1.5% to -0.03%), respectively. The pooled RD for ***dyspnea*** was -6.0% (-7.8% to -4.2%), with event rates in ticagrelor-treated patients ranging between 2.4% and 24%. ***In older ACS patients***, one RCT, specifically designed to evaluate clinically significant bleeding, had an event rate of 24% in the ticagrelor group, and an RD of -5.9% (-11% to -0.9%). The rate of major bleeding was 4% to 8% in the ticagrelol group, and the pooled RD was -2.4% (-4.4% to -0.3%). No studies provided results regarding dyspnea in older ACS patients.

> *Conclusions:* In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor results in a reduced risk of clinically significant bleeding and dyspnea (GRADE ⊕⊕⊕⊕), and may result in little or no difference in the risk of major bleeding but a reduced risk is shown when zero-event trials are excluded (GRADE ⊕⊕◯◯).
>
> In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor probably results in a substantially reduced risk of clinically significant bleeding and a reduced risk of major bleeding (GRADE ⊕⊕⊕◯).

Costs for the assessed treatments are 1 SEK per day for clopidogrel and 21 SEK per day for ticagrelor, resulting in treatment costs for each patient over one year of 365 SEK and 7,700 SEK, respectively. If 80% of the patients in Region Västra Götaland would be prescribed clopidogrel instead of ticagrelor, that is, reversed proportions compared to the current practice, the costs would be reduced by approximately 12 million SEK per year.

Conclusion This HTA shows that clopidogrel, in ACS patients overall, is probably slightly less efficient compared with ticagrelor in reducing the risk of MI and stent thrombosis. For all-cause and CV mortality, clopidogrel may be slightly less efficient or show little or no difference. Regarding adverse effects, use of clopidogrel is favourable, with a reduced risk of clinically significant bleeding and dyspnea. For major bleeding, there may be little or no difference between these DAPT alternatives, or clopidogrel may result in a reduced risk. In older ACS patients, available evidence suggests little or no difference between clopidogrel and ticagrelor regarding all-cause/CV mortality and MI, but the risk of clinically significant bleeding is probably substantially lower with clopidogrel and the risk of major bleeding is probably also lower.

2. Populärvetenskaplig sammanfattning – Swedish summary in plain language

I denna HTA-rapport har vi utvärderat frågeställningen:

- Är klopidogrel likvärdigt med tikagrelor för patienter, inklusive äldre patienter, som behandlas med två blodförtunnande läkemedel efter att ha vårdats för akut koronart syndrom?

Konklusion Enligt vår genomgång av det vetenskapliga underlaget är klopidogrel, för minst 18 år gamla patienter som vårdats för akut koronart syndrom, troligen något sämre än tikagrelor för att förebygga hjärtinfarkt och att förhindra att blodflödet i stenten täpps till. På biverkningssidan är behandling med klopidogrel förknippat med lägre risk för andnöd och blödningar som behöver åtgärdas i sjukvården. Klopidogrel verkar kunna vara något sämre än tikagrelor för att förebygga dödsfall, inklusive de som är hjärt/kärlrelaterade, men när små studier utan dödsfall exkluderas syns ingen sådan skillnad. Klopidogrel verkar kunna vara förknippat med något lägre risk för mycket allvarliga blödningar, men ingen sådan skillnad syns när även små studier utan denna typ av blödningar inkluderas.

För äldre patienter som vårdats för akut koronart syndrom verkar klopidogrel vara likvärdigt med tikagrelor för att förebygga dödsfall, hjärt/kärl-relaterade dödsfall och hjärtinfarkter. Klopidogrel är troligen förknippat med avsevärt lägre risk för blödningar som behöver åtgärdas i sjukvården och innebär troligen även lägre risk för mycket allvarliga blödningar.

Bakgrund Akut koronart syndrom innebär akuta bröstsmärtor som misstänks bero på syrebrist i hjärtat. Syrebristen orsakas av att en/flera blodproppar täpper till kranskärlen. Akut koronart syndrom innefattar både hjärtinfarkt och kärlkramp. Detta är allvarliga tillstånd och kan orsaka död eller bestående skada. I behandlingen ingår att vidga det tilltäppta blodkärlet och att lägga in så kallade stentar för att blodkärlet ska hållas öppet i fortsättningen. För att förhindra att kliniska manifestationer av kranskärlssjukdom återkommer för patienter som vårdats för akut koronart syndrom rekommenderas även behandling med två blodförtunnande läkemedel under 12 månader, bestående av acetylsalicylsyra och antingen tikagrelor eller klopidogrel. Utifrån den så kallade PLATO-studien som publicerades 2009 rekommenderar den europeiska kardiologföreningen tikagrelor som förstahandsalternativ. I PLATO-studien visades tikagrelor vara mer effektivt än klopidogrel som förebyggande behandling, utan att orsaka fler blödningar av hög allvarlighetsgrad.

I Västra Götalandsregionen behandlas mer än 80% av de aktuella patienterna, närmare 3000 individer, med tikagrelor. Övriga utgörs huvudsakligen av personer som behandlas med en annan typ av blodförtunnande behandling, till exempel för att förhindra blodproppar vid förmaksflimmer. I denna situation föredras ofta klopidogrel framför tikagrelor men det saknas tydliga rekommendationer. Sedan PLATO-studien publicerades har metoderna för att återställa blodcirkulationen vid akut koronart syndrom förfinats. Detta skulle kunna påverka den nytta som visats för tikagrelor jämfört med klopidogrel. De patienter som får aktiv behandling är idag också äldre, vilket i sig innebär att risken för blödning ökar, något som skulle kunna ha betydelse för blödningsrisken med klopidogrel respektive tikagrelor som del av den blodförtunnande behandlingen.

Metod Med hjälp av etablerade metoder identifierade vi de vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågeställningen. Vi granskade de enskilda studiernas kvalitet och bedömde tillförlitligheten i de sammanlagda resultaten.

Resultat Denna rapport baseras på 35 studier med 31 389 patienter där de jämförda behandlingsalternativen tilldelats slumpmässigt och 46 studier med 545 537 patienter där behandling ordinerats som del i ordinarie sjukvård.

När man i dessa studier mäter ***alla dödsfall, hälsorelaterad livskvalitet och återinläggning*** kan resultaten sägas spegla nettoeffekten av en läkemedelsbehandling, det vill säga nytta/risk-balansen. När alla studier inkluderas verkar klopidogrel kunna vara något sämre än tikagrelor för att förebygga dödsfall, men när små studier utan dödsfall exkluderas syns ingen skillnad mellan dessa behandlingsalternativ. Att resultaten skiljer sig kan delvis hänföras till meta-analys-tekniska aspekter; små studier utan händelser (i detta fall dödsfall) under uppföljningstiden, i den ena eller båda jämförelsegrupperna, kan av matematiska skäl få förhållandevis stor betydelse för resultaten. Avseende hälsorelaterad livskvalitet och återinläggning var det vetenskapliga underlaget för osäkert för slutsatser. För äldre patienter som vårdats för akut koronart syndrom verkar det inte vara någon skillnad mellan klopidogrel och tikagrelor när det gäller att förebygga dödsfall. Avseende hälsorelaterad livskvalitet och återinläggning saknas studier som fokuserar på den äldre åldersgruppen.

När man i dessa studier mäter ***hjärt/kärl-relaterade dödsfall, hjärtinfarkt, stenttrombos och kärlkramp*** kan resultaten sägas spegla de avsedda effekterna av läkemedelsbehandlingen. Klopidogrel är troligen något sämre på att förebygga hjärtinfarkt och att förhindra att blodflödet i stenten täpps till av en propp. I genomsnitt behöver 125 patienter behandlas med tikagrelor, istället för klopidogrel, för att undvika en (1) hjärtinfarkt. På motsvarande sätt behöver 143 eller 167 patienter (beroende på om studier utan stenttromboser i någon av jämförelsegrupperna inkluderas eller exkluderas) behandlas med tikagrelor för att undvika en (1) tilltäppande propp i stenten. Klopidogrel tycks också vara något sämre än tikagrelor för att förebygga kälkramp. Avseende hjärt/kärl-relaterade dödsfall verkar klopidogrel kunna vara lite sämre än tikagrelor, men när små studier utan sådana dödsfall exkluderas syns ingen skillnad mellan klopidogrel och tikagrelor. För äldre patienter som vårdats för akut koronart syndrom verkar det inte vara någon skillnad mellan klopidogrel och tikagrelor vad gäller hjärt/kärl-relaterade dödsfall och hjärtinfarkt, och det vetenskapliga underlaget avseende propp i stenten är för osäkert för slutsatser. För kärlkramp saknas studier som fokuserar på den äldre åldersgruppen.

När man i dessa studier mäter ***blödningar och andnöd*** kan resultaten sägas spegla riskerna med läkemedelsbehandlingen. Klopidogrel ger, jämfört med tikagrelor och för minst 18 år gamla patienter som vårdats för akut koronart syndrom, lägre risk för blödningar som behöver åtgärdas i sjukvården. I genomsnitt behöver 53 eller 43 patienter (beroende på om studier utan blödningar av denna dignitet i någon av jämförelsegrupperna inkluderas eller exkluderas) behandlas med klopidogrel istället för tikagrelor för att undvika en (1) sådan blödning. Vad gäller mycket allvarliga blödningar verkar klopidogrel kunna vara förknippat med något lägre risk, men detta är osäkert. Klopidogrel innebär lägre risk för andnöd. I genomsnitt behöver 17 patienter behandlas med klopidogrel, istället för tikagrelor, för att undvika ett fall av andnöd. För äldre patienter som vårdats för akut koronart syndrom ger klopidogrel troligen avsevärt lägre risk för blödningar som behöver åtgärdas i sjukvården och innebär troligen även lägre risk för mycket allvarliga blödningar. I genomsnitt behöver 17 respektive 42 äldre patienter behandlas med klopidogrel istället för tikagrelor för att undvika en (1) blödning som behöver åtgärdas i sjukvården respektive en (1) mycket allvarlig blödning.

Kostnaden per behandlad patient för de utvärderade behandlingarna är cirka 1 krona per dag för klopidogrel och 21 kronor per dag för tikagrelor, vilket motsvarar 365 respektive 7700 kronor per år. Om 80% av patienterna i Västra Götalandsregionen skulle behandlas med klopidogrel istället för som idag med tikagrelor, skulle kostnaderna för behandlingen i regionen minska med 12 miljoner kronor per år.

This HTA was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary in plain language is intended for readers who are not familiar with this specific medical field and/or evidence synthesis.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, November 25th 2020 and April 28th 2021.

Regional board for quality assurance of activity-based HTA	
Bergh, Christina	MD, Professor
Bernhardsson, Susanne	PT, Associate professor
Hakeberg, Magnus	OD, Professor
Hongslo Vala, Cecilie	PhD
Jivegård, Lennart	MD, Senior university lecturer
Larsson, Anders	MD, PhD
Nelzén, Olle	MD, Associate professor
Petzold, Max	Statistician, professor
Rylander, Christian	MD, Associate professor
Sjögren, Petteri	DDS, PhD
Sjövall, Henrik	MD, Professor
Skogby, Maria	RN, PhD
Strandell, Annika	MD, Associate professor
Svanberg, Therese	HTA librarian
Svensson, Mikael	Health economist, Professor
Wallerstedt, Susanna	MD, Professor
Wartenberg, Constanze	Psychologist, PhD

DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings

Outcomes	P	Number of RCTs (number of patients)	Absolute effect		Relative effect	Certainty of evidence GRADE
			Outcome rate in ticagrelor group (range)	RD (95% CI) clopidogrel minus ticagrelor[1] Including zero-event RCTs (P1) Excluding zero-event RCTs (P1)	RR (95% CI) clopidogrel versus ticagrelor[1]	
Mortality, all-cause	P1	22 (28,487)	0% to 9%	**0.7% (0.2% to 1.2%)** 0.5% (-0.3% to 1.4%)	**1.24 (1.11 to 1.38)**	⊕⊕◯◯[3]
	P2	2 (1,202)	6.8% to 9%	2.4% (-3.3% to 8.0%)	1.26 (0.82 to 1.93)	⊕⊕◯◯[4]
Mortality, CV	P1	26 (29,935)	0% to 6%	**0.6% (0.2% to 1.0%)** 0.4% (-0.3% to 1.1%)	**1.24 (1.11 to 1.40)**	⊕⊕◯◯[3]
	P2	2 (1,202)	3.0% to 6%	3.9% (-4.8% to 13%)	1.63 (0.80 to 3.29)	⊕⊕◯◯[4]
MI	P1	28 (30,454)	0% to 7.4%	**0.8% (0.4% to 1.3%)** **0.8% (0.03% to 1.5%)**	**1.23 (1.03 to 1.46)**	⊕⊕⊕◯[5]
	P2	2 (1,202)	6% to 7.4%	3.7% (-5.0% to 12%)	1.45 (0.60 to 3.48)	⊕⊕◯◯[4]
Bleeding, clinically significant[2]	P1	8 (25,407)	0% to 24%	**-1.9% (-3.6% to -0.2%)** **-2.3% (-4.0% to -0.5%)**	**0.76 (0.64 to 0.91)**	⊕⊕⊕⊕
	P2	1 (1,002)	24%	**-5.9% (-11% to -0.9%)**	HR: **0.71 (0.54 to 0.94)**	⊕⊕⊕◯[6]
Bleeding, major	P1	26 (29,553)	0% to 10%	-0.2% (-0.6% to 0.2%) **-0.8% (-1.5% to -0.03%)**	**0.80 (0.66 to 0.98)**	⊕⊕◯◯[7]
	P2	2 (1,202)	4% to 8%	**-2.4% (-4.4% to -0.3%)**	**0.53 (0.28 to 0.97)**	⊕⊕⊕◯[8]
Stent thrombosis	P1	18 (16,629)	0% to 1.3%	**0.7% (0.4% to 1.1%)** **0.6% (0.02% to 1.0%)**	**1.75 (1.28 to 2.39)**	⊕⊕⊕◯[9]
	P2	1 (1,002)	0%	**1% (0.05% to 2.0%)**	N/A	⊕◯◯◯[10]
Angina	P1	4 (667)	0% to 8%	**6.5% (2.9% to 10%)**	**2.70 (1.39 to 5.23)**	⊕⊕◯◯[11]
	P2	0				
Rehospitalisation	P1	4 (389)	3% to 5%	3.4% (-0.9% to 7.8%)	2.08 (0.85 to 5.07)	⊕◯◯◯[12]
	P2	0				
HRQL	P1	1 (15,212)	EQ-5D: 0.863 vs 0.864, P=0.69		N/A	⊕◯◯◯[13]
	P2	0				
Dyspnea	P1	15 (25,017)	2.4% to 24%	**-6.0% (-7.8% to -4.2%)** **-6.0% (-8.3% to -3.9%)**	**0.56 (0.52 to 0.61)**	⊕⊕⊕⊕
	P2	0				

CI = confidence interval, CV = cardiovascular, EQ-5D = EuroQol 5 dimensions, HRQL = health-related quality of life, MI = myocardial infarction, N/A = not applicable, P = patients, P1 = ACS patients subjected to DAPT, P2 = older ACS patients subjected to DAPT, RD = risk difference, RR = risk ratio

Footnotes:
[1]Results not including the line of unity are bolded, representing a statistically significant difference between the comparison groups
[2]Clinically significant bleedings included major bleedings and bleedings requiring surgical or medical intervention.
[3]Serious inconsistency, some study limitations, some indirectness
[4]Serious imprecision, some study limitations, some indirectness
[5]Some indirectness, some inconsistency
[6]Some imprecision, uncertainty regarding consistency
[7]Serious study limitations, serious inconsistency
[8]Some imprecision
[9]Serious indirectness
[10]Serious study limitations, serious imprecision, some indirectness
[11]Serious study limitations, serious indirectness
[12]Serious study limitations, serious indirectness, serious imprecision
[13]Serious study limitations, serious imprecision, some indirectness, some inconsistency

Certainty of evidence according to GRADE

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ACS = acute coronary syndrome
ADP = adenosine diphosphate
AMI = acute myocardial infarction
AP = angina pectoris
ASA = acetylsalicylic acid
BARC = bleeding academic research consortium
BMS = bare-metal stent
C = control
CABG = coronary artery by-pass grafting
CV = cardiovascular
CYP = cytochrome P450
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
EQ-5D = EuroQol 5 dimensions
FFR = fractional flow reserve
HRQL = health-related quality of life
I = intervention
IVUS = intravascular ultrasound
MACE = major adverse cardiovascular events
MI = myocardial infarction
Non-RCT = non-randomized controlled trial
NR = not reported
NSTE-ACS = non-ST-elevation acute coronary syndrome
NSTEMI = non-ST-elevation myocardial infarction
OCT = optical coherence tomography
OR = odds ratio
P2Y12 = a chemoreceptor for adenosine diphosphate
PCI = percutaneous coronary intervention
PLATO = the pivotal study of platelet inhibition and patient outcome for ticagrelor
PS = propensity score
QALY = quality adjusted life-year
RCT = randomised controlled trial
SCAAR = Swedish Coronary Angiography and Angioplasty Registry
SPC = summary of product characteristics
STEMI = ST-elevation myocardial infarction
TIA = transient ischemic attack
TIMI = thrombolysis in myocardial infarction bleeding classification (also used for grading of coronary blood flow)
TVR = target vessel revascularisation
UAP = unstable angina pectoris

5. Background

Disease/disorder of interest and its degree of severity

Worldwide, acute coronary syndrome (ACS) is a major health problem. Since the condition and its complications may result in premature death and permanent illness, the condition has a high degree of severity. Almost half of all deaths due to coronary heart disease occur following an ACS (Go et al., 2013, Thom et al., 2006).

The most common mechanism behind ACS is a rupture of an atherosclerotic plaque, resulting in a partial or complete occlusion of a coronary artery. The plaque disruption exposes subendothelial collagen, resulting in the activation of platelets and the coagulation cascade which, in turn, may lead to thrombus formation and partial or complete obstruction of the coronary vessel blood flow (Naghavi et al., 2003, Burke et al., 2001). The reduced blood flow due to coronary occlusion results in an ACS, commonly accompanied by symptoms of ischemia such as chest pain or discomfort, dyspnea, often combined with other symptoms such as nausea, cold sweat or general fatigue. Patients with a complete coronary occlusion often present with ST-segment elevation myocardial infarction (STEMI), which can lead to a transmural infarction (Burke et al., 2001). Early reperfusion with either pharmacological treatment or percutaneous coronary intervention (PCI) in patients with STEMI is well known to reduce mortality and morbidity (Nallamothu et al., 2015). Patients with partially occluded coronary arteries often lack ST-segment elevation (Burke, 2001). These patients are classified as having non-STEMI (NSTEMI) or unstable angina pectoris (UAP), depending on whether they have or do not have signs of myocardial injury, for instance increased troponin levels in blood samples. Most of these patients undergo coronary angiography and when suitable PCI sub-acute, which also have well-documented reduction of mortality and morbidity (Wallentin et al., 2016).

Prevalence and incidence

According to the Swedish Coronary Angiography and Angioplasty Registry (SCAAR, Tillberg, 2020), 2,758 patients in Region Västra Götaland underwent coronary angiography in 2019 because of ACS. About 30% of these patients are 75 years or older (Völz et al., 2020). In addition to the numbers described above, there are a few patients with ACS who are not referred to angiography. Patients not referred are mainly older people and/or those suffering from multiple and severe health problems, and invasive treatment is not provided because no benefit of such an intervention is expected. According to a national quality register, about 90% of ACS patients below 80 years of age are investigated with coronary angiography (Tillberg, 2020).

Present treatment

After hospitalisation for ACS, with or without ST-segment elevation, dual antiplatelet therapy (DAPT) is usually prescribed for 12 months to prevent further cardiovascular (CV) events, mainly ticagrelor or clopidogrel combined with acetylsalicylic acid (ASA). In Region Västra Götaland, about 2,200 ACS patients (83% of all) are treated with new P2Y12 inhibitors (Tillberg, 2020), that is, ticagrelor or prasugrel. Since very few patients receive prasugrel, almost all of these patients are prescribed ticagrelor. About 470 (17%) patients are treated with clopidogrel. The majority of the latter patients are also being treated with a direct-acting oral anticoagulant or warfarin. After 12 months of DAPT, almost all patients continue with ASA alone.

PCI procedure

The PCI procedure has undergone improvements over time. For example, in PLATO, more than one-third of the study population was not treated with PCI and more than 40% of those treated with PCI received a bare-metal stent (BMS) (Wallentin et al., 2009).
Today there is no routine use of BMS in Sweden due to the better outcomes with drug-eluting stents (DES) (Tillberg, 2020, Palmerini et al., 2015.) Furthermore, improvements in the periprocedural

treatment has taken place such as high use of radial access, low use of glycoprotein IIb/IIIa–blockers, high implantation rates of modern DES and increase in use of invasive diagnostic methods such as fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT) (Tillberg, 2020, Palmerini et al., 2015). These improvements in the procedure may alter the benefit-risk balance between bleeding and thromboembolic events.

Present recommendations from medical societies or health authorities

Current guidelines by the European Society of Cardiology recommend DAPT over a 12-month period after ACS. In addition to ASA, both prasugrel (loading dose: 60 mg per os (p.o.), followed by a maintenance dose: 10 mg p.o. once daily) and ticagrelor (loading dose: 180 mg p.o., maintenance dose: 90 mg p.o. twice daily) are recommended P2Y12 receptor inhibitor alternatives. Clopidogrel (loading dose: 300 mg p.o., maintenance dose: 75 mg p.o. once daily) is recommended only if ticagrelor or prasugrel are not available or contraindicated (Neuman et al., 2019). For patients concurrently treated with a direct-acting oral anticoagulant or warfarin, clopidogrel is primarily chosen, however there are no clear recommendations regarding DAPT in combination with anti-coagulants. According to regional guidelines, either clopidogrel or ticagrelor, combined with ASA, is recommended after ACS (REKlistan, 2021).

6. Health Technology at issue: Clopidogrel

Clopidogrel is an adenosine diphosphate (ADP) receptor antagonist which inhibits platelet aggregation. In 1998, the European Commission issued a marketing authorisation for the prevention of atherothrombotic events in patients suffering from myocardial infarction, ischaemic stroke or established peripheral arterial disease. In 2003, NSTE-ACS was added to the indications, and in 2006, STEMI was also explicitly included.

Since the pivotal study of ticagrelor in patients with ACS (PLATO; Wallentin et al., 2009), where ticagrelor was superior to clopidogrel regarding the primary composite endpoint of vascular death, non-fatal myocardial infarction (MI) and stroke without leading to an increased risk of major bleeding, this P2Y12 inhibitor has widely been regarded as the best treatment alternative. Ticagrelor is a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, whereas clopidogrel is a prodrug, requiring transformation to the active metabolite via the cytochrome P450 system (CYP2C19), and is an irreversible P2Y12 inhibitor (Storey et al., 2007, Husted et al., 2006). The rationale for the PLATO trial was that the efficacy of clopidogrel could be affected by slow and variable transformation to the active metabolite which, in turn, could lead to modest and variable platelet inhibition and increased risk of thrombotic complications (Jernberg et al., 2006). The exclusive market authorisation is expected to expire in 2024.

The PLATO trial recruited patients more than ten years ago, and the acute treatment of ACS has undergone changes in many respects during this time period. Hence, it is uncertain whether the PLATO results are applicable to all patients in current clinical practice. For example, only about 60% of the PLATO population were treated with PCI and about 40 % received a BMS (Wallentin et al., 2009). In current praxis, about 80% of ACS patients undergo PCI, and the use of DES is almost 100% (Tillberg, 2020). Furthermore, the diagnostic tools, for example intravascular imaging and physiologic evaluations used during coronary angiography, have been enhanced.

The beneficial effect of ticagrelor, compared with clopidogrel, in the PLATO trial was at the expense of the safety endpoint; although the rate of major bleedings was similar in the randomisation groups, more bleeding complications that did not fulfil this definition were seen in the ticagrelor group. With age, the risk of bleeding increases (Costa et al., 2017). Consequently, the fact that ACS patients today

are older than the PLATO population may be important regarding the benefit-risk balance of the two treatment alternatives. Indeed, according to SCAAR data on PCI patients in Region Västra Götaland, the mean age is 67 years and about 30% of the patients are 75 years of age or older (Völz et al., 2020). In the PLATO trial, the mean age was 62 years and 15% were 75 years or older. The increased age in the population at issue for 12-month maintenance DAPT, combined with improved PCI procedures, could be of importance for the benefit-risk balance of the two P2Y12 receptor inhibitors clopidogrel and ticagrelor.

7. Focused question

In ACS patients subjected to DAPT, including those of older age, is clopidogrel combined with ASA similar to ticagrelor combined with ASA, regarding the outcomes mortality, MI, bleeding, stent thrombosis, angina, rehospitalisation, health-related quality of life (HRQL), and dyspnea?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P P1: Adult (>18 years) patients subjected to DAPT in ACS (MI with or without ST elevation, unstable angina)

P2: Older (>65 years) patients subjected to DAPT in ACS (MI with or without ST elevation, unstable angina)

I Clopidogrel + ASA

C Ticagrelor + ASA

O Critical for decision-making

- Mortality (all-cause, cardiovascular)
- MI
- Bleeding (clinically significant, major)
- Stent thrombosis
- Angina

Important for decision-making

- Rehospitalisation
- Health related quality of life (HRQL)
- Dyspnea

Restricted to:

- Randomised controlled trial
- Non-randomised controlled trials including >500 patients
- Studies written in English, Swedish, Danish or Norwegian
- Studies published from 2005 onwards

8. Methods

Systematic literature search (Appendix 1)

During September 2019, with an update in September 2020, two authors (AL, IS) performed systematic searches in PubMed, Embase, Medline and the Cochrane Library. The websites of the Swedish Agency for Health Technology Assessment and Assessment of Social Service (SBU) and Folkehelseinstituttet were searched, and reference lists of relevant articles were scrutinised for additional references. The HTA was entered in PROSPERO in May 2020, and was registered in July 2020 (CRD42020184622). Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. The above mentioned authors independently of one another assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. The selected articles were sent to all authors, who independently read the articles. In a consensus meeting, the authors decided which articles to include in the HTA. Any disagreements were resolved in consensus. The excluded studies, including reasons for exclusions, are presented in Appendix 3.

Critical appraisal

The included studies and their design as well as patient characteristics are presented in Appendix 2. Data were extracted and checked by at least two authors.

Included studies were critically appraised using the checklists for assessment of randomised controlled trials (RCT) and non-RCTs provided by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU). For the assessments of directness and precision, a modified checklist from a prior version of the SBU checklist was used. In Appendices 4.1-8, the results and the quality of each study are summarised per outcome. The assessments regarding directness and study quality (risk of bias) are summarised in Appendix 5.

Meta-analyses

We compared clopidogrel with ticagrelor, i.e. the reverse of what is usually seen for this comparison. The rationale for this approach was that ticagrelor is the control, having become standard treatment after the PLATO trial, and clopidogrel is the intervention.

In the initial analysis plan, we decided that meta-analyses would be conducted separately for RCTs and for non-RCTs reporting either adjusted hazard ratios or hazard ratios between matched groups. We also decided that the main meta-analyses, forming the primary basis for our conclusions, would be based on RCTs without major risk of bias and without major problems regarding directness. This approach appeared problematic as it restricted the meta-analyses to few RCTs with substantial clinical diversity. Therefore, we decided that our conclusions would primarily be based on meta-analyses of all RCTs, and to include sensitivity meta-analyses to investigate the robustness of the results, in line with the Cochrane handbook for systematic reviews of interventions, version 6.1. The sensitivity meta-analyses included aspects related to directness and risk of bias, as well as methodological aspects related to meta-analyses. For efficacy outcomes, we also included a sensitivity meta-analysis restricted to RCTs of particular interest for this HTA, i.e. trials comparing approved doses of both clopidogrel and ticagrelor (in accordance with the summary of product characteristics (SPC)) in relevant populations recruited after the PLATO trial, and without the analytically problematic zero-event arm/s/ (described below and in Appendix 6).

Random-effects meta-analyses, including presentation in forest plots, were performed using RevMan 5.3. We chose to focus on absolute risk differences, with 95% confidence intervals (CI). This measure may be particularly useful in decision-making as it reflects the size of the risk increase/decrease.

In Revman, the absolute risk difference is expressed as “Risk difference” and represents the difference between the risk in the clopidogrel group and the ticagrelor group. To assess potential publication bias, funnel plots were used.

Our PICO definition resulted in the inclusion of several small RCTs with zero-event arms. The handling of such studies in meta-analyses is problematic. One alternative is to use continuity correction, an approach that can be questioned as it adds data that do not exist and introduces a bias where zero-event studies receive more weight at the expense of large studies where events occur in both randomisation groups. Another alternative is to leave these trials out, an approach that can also be questioned as some of the available information is disregarded. For further details, see Appendix 6. Since both approaches have drawbacks, we decided to present meta-analyses based on RCTs with and without zero-event trials. We decided to include both alternatives in the conclusion for outcomes where discordant results were obtained with and without inclusion of zero-event trials. Forest plots of meta-analyses with and without zero-event trials were presented in Appendix 6. In the main report, the results without zero-event trials were included in the table of sensitivity analyses.

Certainty of evidence

Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (pages 9-10). The certainty of evidence was assessed according to GRADE (Atkins et al., 2004) and based on RCTs, with reasons for downgrading described in text.

Ongoing research

A search in Clinicaltrials.gov (September 2, 2020) using the search terms (Clopidogrel AND Ticagrelor) AND (NSTEMI OR STEMI OR "Acute Coronary Syndrome" OR infarction OR "Unstable angina" OR "Prinzmetals angina") identified 144 trials.

9. Results

Search results and study selection (Appendix 1)

After removal of duplicates, the literature search identified 3,102 articles (Appendix 1). Two authors (A.L., I.S.) excluded 2,848 publications at the abstract level, and another 101 after full-text reading. The remaining 153 articles were sent to all authors for inclusion/exclusion according to PICO, and 82 articles were finally included in the HTA (Appendix 2). The 71 excluded articles are reported with reasons for exclusion in Appendix 3.

Included studies

This HTA was based on 35 RCTs and 46 non-RCTs. A total of 36 RCT publications were included as outcomes relevant for this HTA from the PLATO trial were published in two papers (Wallentin et al., 2009, Levin et al., 2013).

A total of 31,389 patients were included in all RCTs, and 12,104 patients in RCTs performed after the PLATO trial. Nine RCTs included patients from non-Asian countries (Alexopoulos et al., 2015, Angiolillo et al., 2016, Berwanger et al., 2019, Cannon et al., 2007, Dehghani et al., 2017, Gasecka et al., 2020, Gimbel et al., 2020, Mohareb et al., 2020, Wallentin et al., 2009/Levin et al., 2013). Six RCTs used other doses than the standard ones (Alexopoulos et al., 2015, Gu et al., 2017, Li et al., 2015, Liu et al., 2019a, Xiong et al., 2015, Zhang et al., 2016). Fourteen RCTs had less than 6-month follow-up, spanning from in-hospital ACS care to up to 3 months (Alexopoulos et al., 2015, Angiolillo et al., 2016, Cannon et al., 2007, Cao et al., 2019, Dehghani et al., 2017, Gu et al., 2017, Jing et al., 2016, Kim et al., 2018, Liu et al., 2017, Liu et al., 2019a, Wang et al., 2016b, Xiong et al., 2015, Xue et al., 2016, Yun et al., 2017). Fifteen RCTs were assessed to have major risk of bias (Alexopoulos et al., 2015, Cao et al., 2019, Gu et al., 2017, Jing et al., 2016, Li et al., 2015, Li et al., 2018, Liu et al., 2019a, Wang et al., 2016b, Xiong et al., 2015, Xue et al., 2016, Yang et al., 2018, Yang et al., 2020, You et al., 2020, Yun et al., 2017, Zhang et al., 2016).

A total of 545,537 patients were included in the non-RCTs. Seven non-RCTs included patients from multiple countries (De Filippo et al., 2019, Giordana et al., 2016, Krackhardt et al., 2020, Ohman et al., 2017, Peyracchia et al., 2020, Welsh et al., 2019, Yan et al., 2016,) and five used data from Sweden only (Edfors et al., 2018, Hansson et al., 2016, Sahlen et al., 2016, Szummer et al., 2020, Völz et al., 2020). Eleven non-RCTs including 155,785 patients had no/minor or some problems regarding risk of bias (Ahn et al., 2020, Blin et al., 2019, Peyracchia et al., 2020, Sim et al., 2018, Spoendlin et al., 2018, Sun et al., 2019, Szummer et al., 2020, Turgeon et al., 2020, Wang et al., 2018, Völz et al., 2020, Yun et al., 2019), the remaining 35 non-RCTs having major quality problems (Appendix 5).

P1: all patients, results per outcome

Mortality (Appendix 4.1)

In all, 33 RCTs including 31,267 patients, and 39 non-RCTs including 512,188 patients, provided results regarding mortality. As all-cause mortality can be considered to reflect the benefit-risk balance of treatment and CV mortality the intended benefits of treatment, we decided to analyse these outcomes separately.

All-cause mortality

A total of 22 RCTs including 28,481 patients reported results regarding all-cause mortality in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of all-cause mortality in the ticagrelor group ranged between 0% and 9%. The meta-analysis of all RCTs revealed an absolute risk difference of 0.7% (0.2% to 1.2%) favouring ticagrelor (Figure 1). A significant difference was not evident in all sensitivity analyses (Table 1). The funnel plot illustrated

that publication bias cannot be fully excluded (Figure 2). When 8 RCTs with at least one zero-event arm were excluded (contributing 5 (0.4%) out of a total of 1,294 events), the pooled absolute risk difference was 0.5% (-0.3% to 1.4%) (Appendix 6).

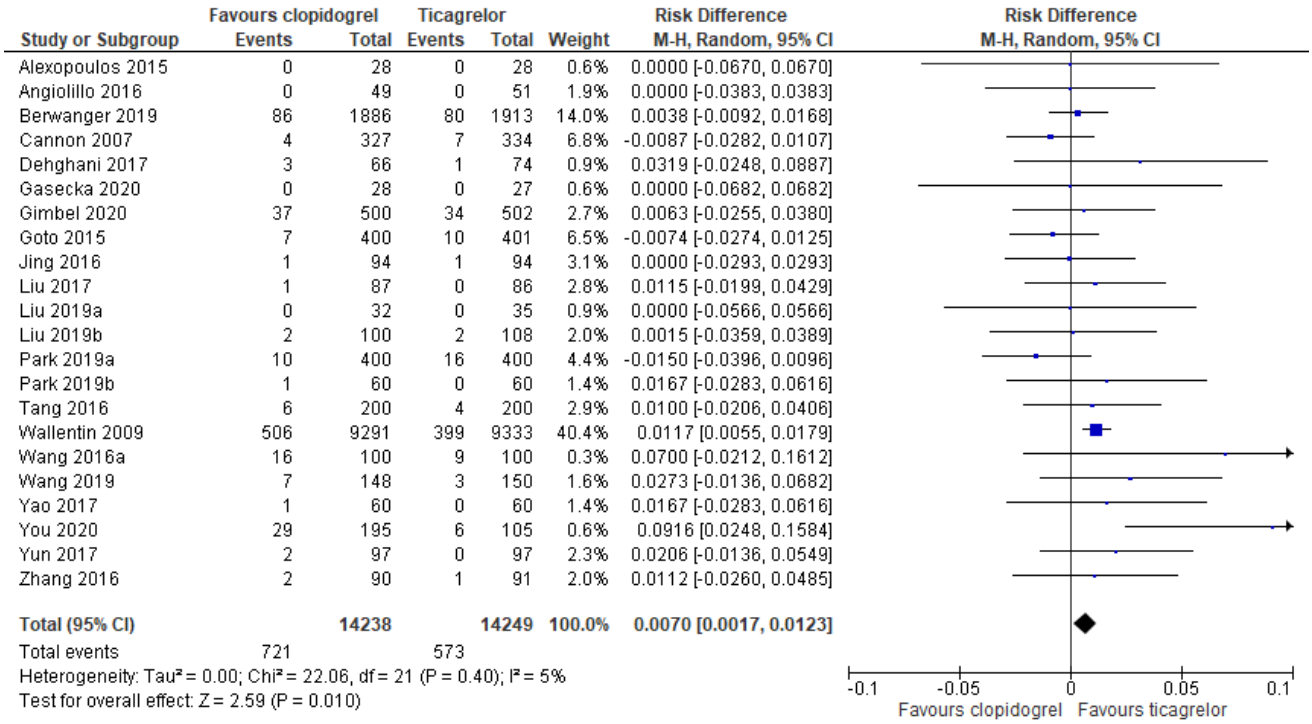


Figure 1 Forest plot and meta-analysis of RCTs providing results regarding all-cause mortality.

Table 1 Sensitivity analysis regarding all-cause mortality. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	22	28,487	**0.7% (0.2% to 1.2%)**
P	Including patients from non-Asian countries	8	24,437	**0.9% (0.4% to 1.4%)**
I/C	Dosing according to SPC	19	28,183	0.6% (-0.03% to 1.3%)
O	Recruited after PLATO	20	9,196	0.5% (-0.2% to 1.2%)
	Follow-up 6-12 months	14	26,908	0.7% (-0.1% to 1.5%)
Analysis	RR	18	28,209	**1.24 (1.11 to 1.38)**
	Only trials with ≥1 event in each randomisation group	14	27,602	0.5% (-0.3% to 1.4%)
	Not major risk of bias	16	27,501	**0.8% (0.3% to 1.2%)**
RCTs restricted to those particularly relevant to this HTA	Dosing according to SPC Recruited after PLATO No outlier populations* Only trials with ≥1 event in each randomisation group	9	7,636	0.2% (-0.7% to 1.0%)

*Outlier populations observed in the funnel plot (Figure 2), found to have a feature in common that diverge from all other studies: event rate >10% in the clopidogrel group.

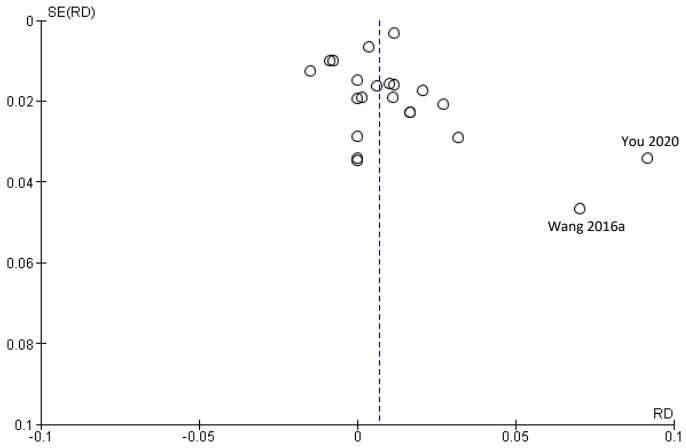


Figure 2 Funnel plot of RCTs providing results regarding all-cause mortality.

A total of 37 non-RCTs including 502,495 patients reported results regarding all-cause mortality in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 21 of these (350,569 patients) reported either adjusted hazard ratios regarding all-cause mortality or hazard ratios between matched groups, resulting in a pooled hazard ratio of 1.23 (1.13 to 1.35) favouring ticagrelor (Figure 3).

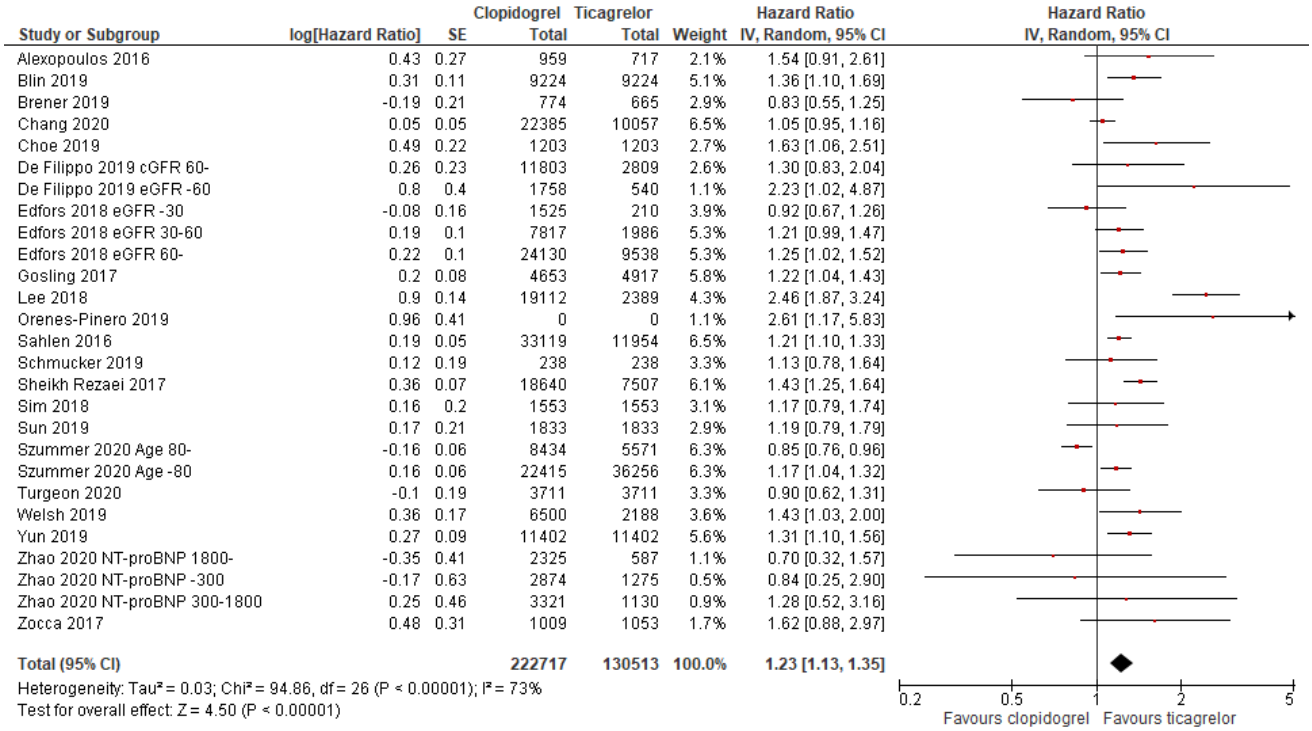


Figure 3 Forest plot and meta-analysis of non-RCTs providing poolable results regarding all-cause mortality.

In the GRADE process, we downgraded one step because of serious inconsistency; the sensitivity analyses did not confirm robustness of the main results. GRADE was downgraded one additional step because of a combination of some study limitations and some indirectness. Study limitations included the bias introduced in the meta-analysis by zero-event RCTs, and all RCTs had directness issues.

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may be slightly less efficient in reducing the risk of all-cause mortality, but shows little or no difference when zero-event trials are excluded (low certainty of evidence, GRADE ⊕⊕◯◯).*

CV mortality

A total of 26 RCTs including 29,935 patients reported results regarding CV mortality in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of CV mortality in the ticagrelor group ranged between 0% and 6%. The meta-analysis of all RCTs revealed an absolute risk difference of 0.6% (0.2% to 1.0%) favouring ticagrelor (Figure 4), a significant difference not being evident in some of the sensitivity analyses (Table 2). The funnel plot illustrated that publication bias cannot be fully excluded (Figure 5). When 13 RCTs with at least one zero-event arm were excluded (contributing 9 (0.8%) out of a total of 1,117 events), the pooled absolute risk difference was 0.4% (-0.3% to 1.1%) (Appendix 6).

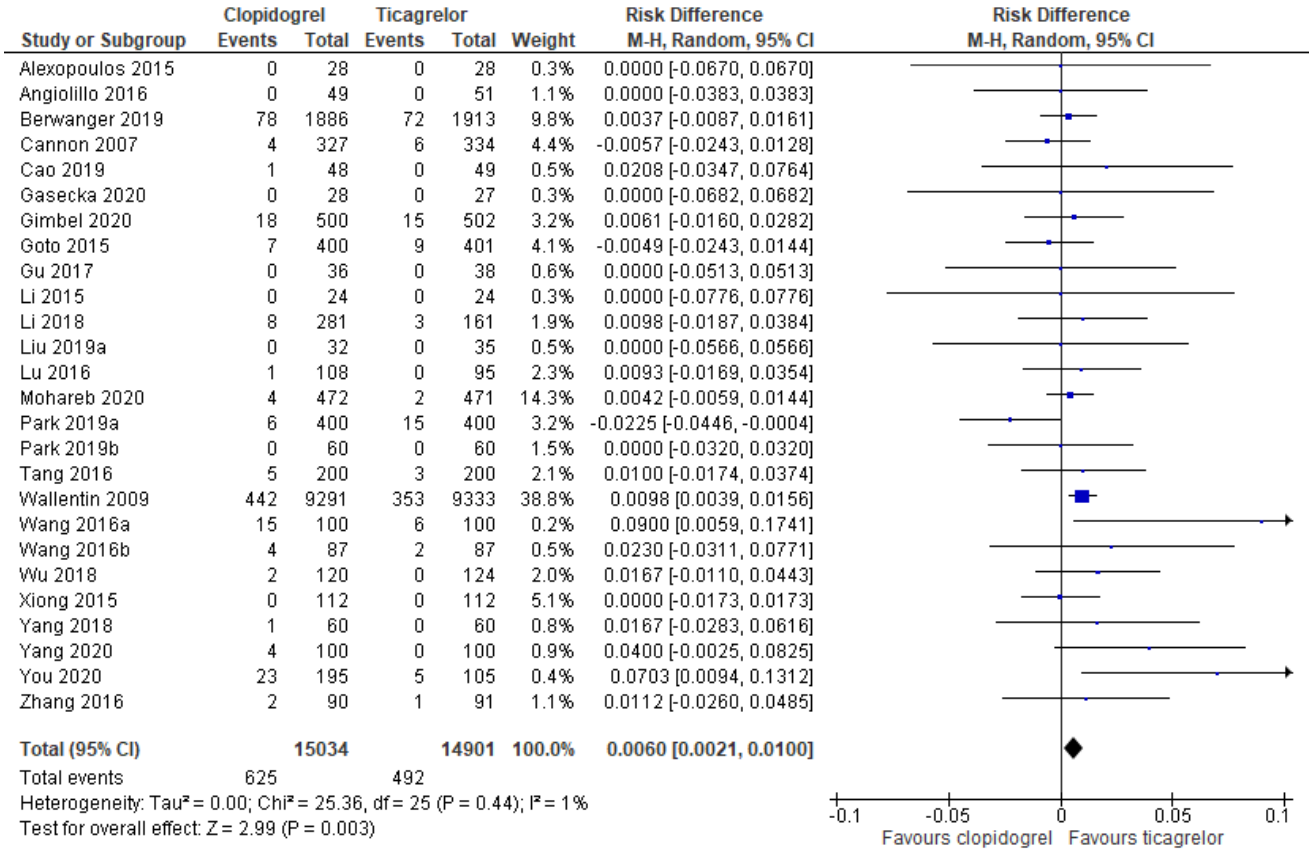


Figure 4 Forest plot and meta-analysis of RCTs providing results regarding CV mortality.

Table 2 Sensitivity analysis regarding CV mortality. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	26	29,935	**0.6% (0.2% to 1.0%)**
P	Including patients from non-Asian countries	8	25,240	**0.7% (0.2% to 1.1%)**
I/C	Dosing according to SPC	20	29,285	**0.6% (0.01% to 1.1%)**
O	Recruited after PLATO	24	10,650	0.4% (-0.1% to 1.0%)
	Follow-up 6-12 months	18	28.482	**0.6% (0.1% to 1.2%)**
Analysis	RR	18	29,191	**1.24 (1.11 to 1.40)**
	Only trials with ≥1 event in each randomisation group	13	28,327	0.4% (-0.3% to 1.1%)
	Not major risk of bias	14	27,952	0.4% (-0.2% to 1.0%)
RCTs restricted to those particularly relevant to this HTA	Dosing according to SPC Recruited after PLATO No outlier populations* Only trials with ≥1 event in each randomisation group	8	8,361	0.2% (-0.4% to 0.8%)

*Outlier populations observed in the funnel plot (Figure 5), found to have a feature in common that diverge from all other studies: event rate >10% in the clopidogrel group.

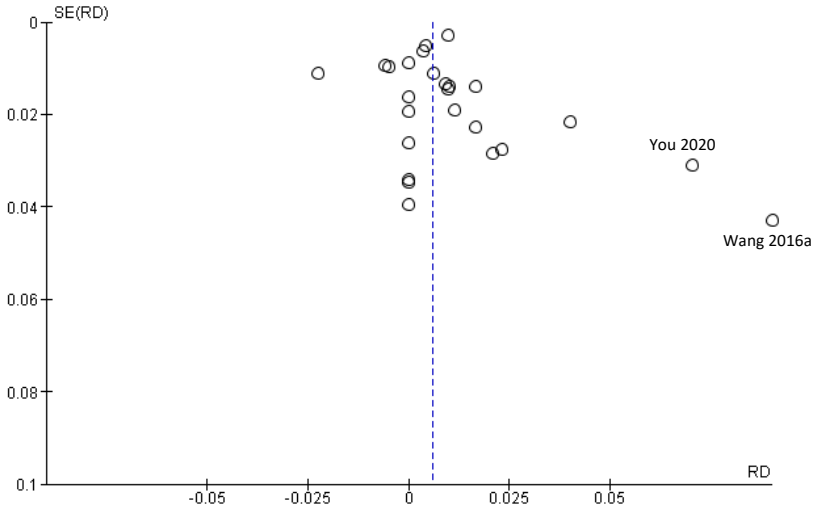


Figure 5 Funnel plot of RCTs providing results regarding CV mortality.

A total of 11 non-RCTs including 65,563 patients reported results regarding CV mortality in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 6 non-RCTs (40,577 patients) reported either adjusted hazard ratios regarding CV mortality or hazard ratios between matched groups, resulting in a pooled hazard ratio of 1.43 (1.17 to 1.74) favouring ticagrelor (Figure 6).

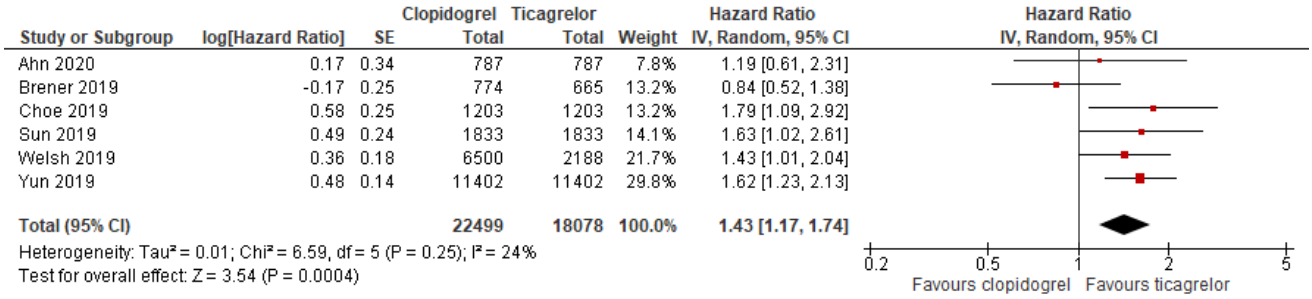


Figure 6 Forest plot and meta-analysis of non-RCTs providing poolable results regarding CV mortality.

In the GRADE process, we downgraded one step because of serious inconsistency; the sensitivity analyses did not confirm robustness of the main results. GRADE was downgraded one additional step because of a combination of some study limitations and some indirectness. Study limitations included the bias introduced in the meta-analysis by zero-event RCTs, and all RCTs had directness issues.

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may be slightly less efficient in reducing the risk of CV mortality, but shows little or no difference when zero-event trials are excluded*
> *(low certainty of evidence, GRADE ⊕⊕◯◯).*

Myocardial infarction (Appendix 4.2)

A total of 28 RCTs including 30,454 patients reported results regarding MI in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of MI in the ticagrelor group ranged between 0% and 7.4%. The meta-analysis of all RCTs revealed an absolute risk difference of 0.8% (0.4% to 1.3%) favouring ticagrelor (Figure 7), which was robust over the sensitivity analyses (Table 3). The funnel plot illustrated that publication bias cannot be fully excluded (Figure 8). When 11 RCTs with at least one zero-event arm were excluded (contributing 9 (0.6%) out of a total of 1,480 events), the pooled absolute risk difference was 0.8% (0.03% to 1.5%) (Appendix 6).

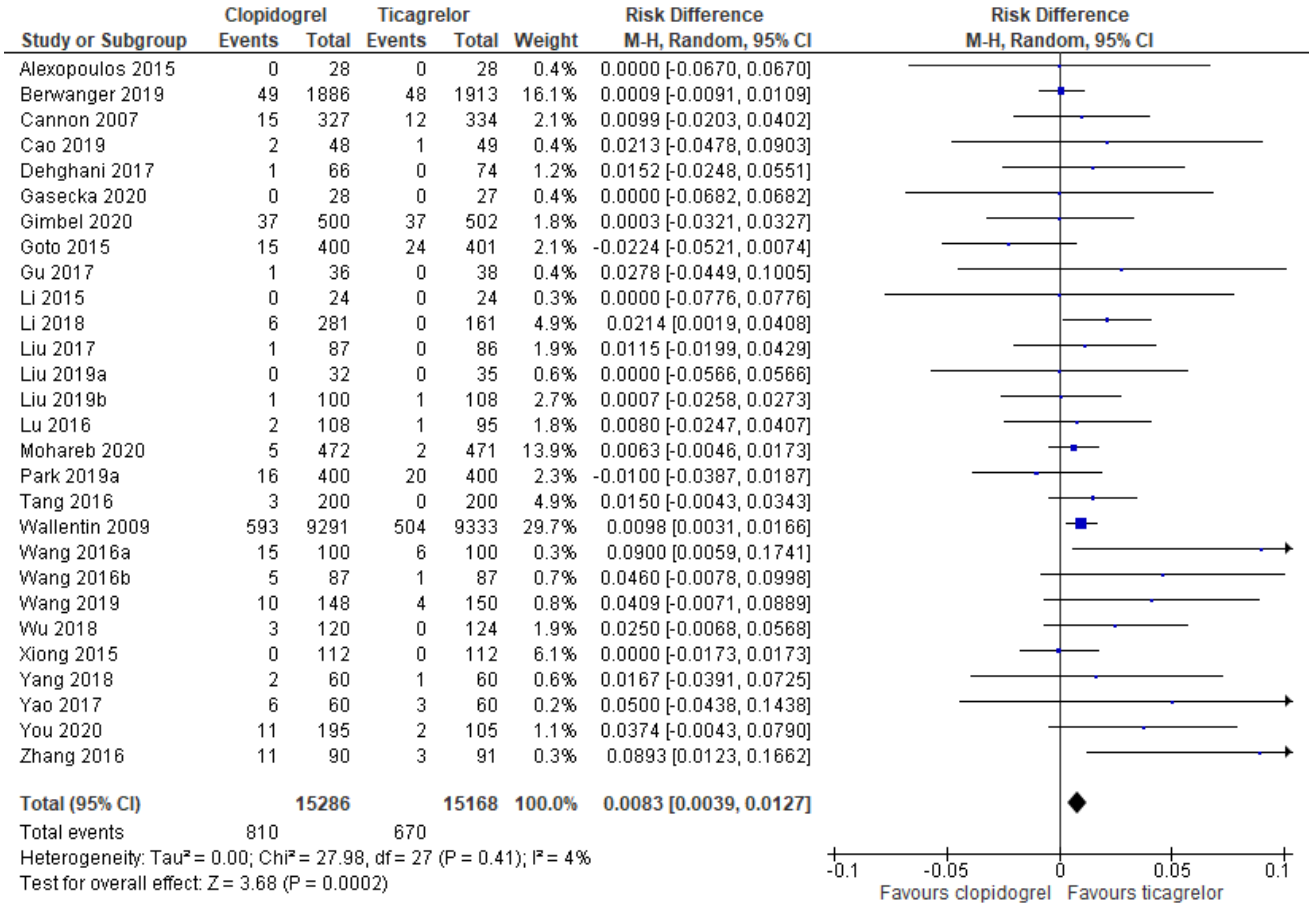


Figure 7 Forest plot and meta-analysis of RCTs providing results regarding MI.

Table 3 Sensitivity analysis regarding MI. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	28	30,454	**0.8% (0.4% to 1.3%)**
P	Including patients from non-Asian countries	8	25,280	**0.7% (0.2% to 1.2%)**
I/C	Dosing according to SPC	22	29,804	**0.9% (0.4% to 1.3%)**
O	Recruited after PLATO	26	11,169	**0.8% (0.2% to 1.4%)**
	Follow-up 6-12 months	19	28,788	**0.9% (0.3% to 1.5%)**
Analysis	RR	23	30,004	**1.23 (1.03 to 1.46)**
	Only trials with ≥1 event in each randomisation group	17	28,531	**0.8% (0.03% to 1.5%)**
	Not major risk of bias	17	28,671	**0.7% (0.3% to 1.2%)**
RCTs restricted to those particularly relevant to this HTA	Dosing according to SPC Recruited after PLATO No outlier populations* Only trials with ≥1 event in each randomisation group	13	8,865	0.4% (-0.3% to 1.2%)

*Outlier populations observed in the funnel plot (Figure 8), found to have a feature in common that diverge from all other studies: event rate >10% in the clopidogrel group.

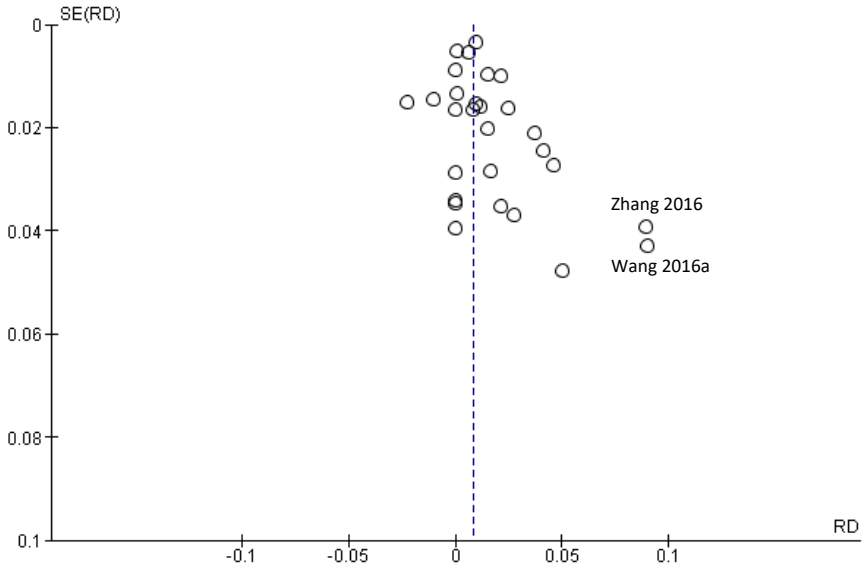


Figure 8 Funnel plot of RCTs providing results regarding MI.

A total of 35 non-RCTs including 388,294 patients reported results regarding MI in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 14 non-RCTs (264,990 patients) reported either adjusted hazard ratios regarding CV mortality or hazard ratios between matched groups, resulting in a pooled hazard ratio of 1.12 (1.02 to 1.22) favouring ticagrelor (Figure 9).

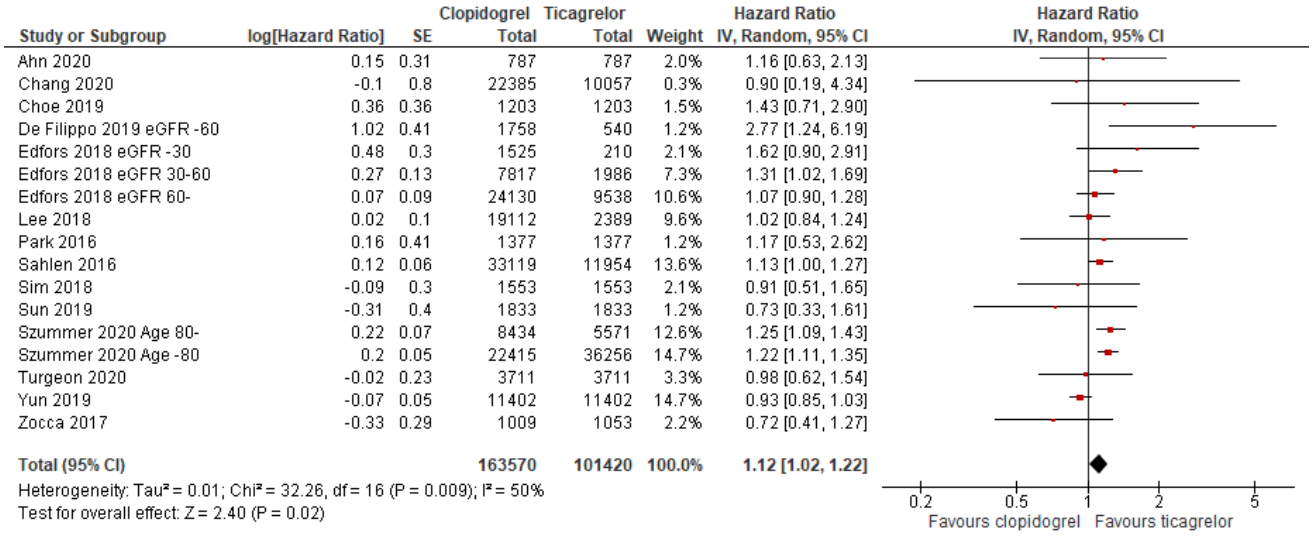


Figure 9 Forest plot and meta-analysis of non-RCTs providing poolable results regarding MI.

In the GRADE process, we downgraded one step because of the combination of some inconsistency and some indirectness. As the RCTs that were either double-blind or single-blind with blinded outcome assessments had varying results, we considered the results somewhat inconsistent; one study did not cross the line of unity favouring ticagrelor (Wallentin et al., 2009), whereas four others had point estimates close to 0 (Berwanger et al., 2019, Gimbel et al., 2020) or below 0 (Goto et al., 2015, Park et al., 2019a). All RCTs had directness issues.

Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor is probably slightly less efficient in reducing the risk of MI (moderate certainty of evidence, GRADE ⊕⊕⊕◯).

Bleeding (Appendix 4.3)

In all, 31 RCTs including 30,489 patients, and 40 non-RCTs including 498,943 patients, provided results regarding bleedings in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. Different bleeding scales were used in the included studies. The definitions of categories within commonly used scales are described in Table 4.

Table 4 Definitions of categories of bleeding in the BARC, PLATO, and TIMI bleeding scales (Mehran et al., 2011).

Bleeding scale	Categories	Definition
BARC	1	Not actionable
	2	Actionable, requires diagnostic studies, hospitalisation, or treatment by a health care professional
	3	a. Overt bleeding + Hb drop 3-5 g/dL; overt bleeding + transfusion b. Overt bleeding + Hb drop >5 g/dL; cardiac tamponade; bleeding requiring surgical intervention; bleeding requiring intravenous vasoactive agents c. Intracranial haemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleeding compromising vision
	4	CABG-related bleeding
	5	Fatal bleeding
PLATO	Major	Fatal; intracranial; intrapericardial with cardiac tamponade; resulting in hypovolemic shock or severe hypotension that requires pressors or surgery; overt bleeding + Hb drop >3 g/dL; requiring transfusion ≥2 units; significantly disabling (e.g. intraocular with permanent vision loss)
	Minor	Requiring medical intervention
	Minimal	Not requiring intervention
TIMI (non-CABG-related bleeding)	Major	Intracranial bleeding; overt bleeding + Hb drop ≥5 g/dL; fatal bleeding
	Minor	Overt bleeding + Hb drop 3-5 g/dL
	Requiring medical attention	Overt bleeding not meeting major or minor criteria + any of a-c below: a. requiring medical or surgical intervention b. leading to or prolonging hospitalisation c. prompting evaluation, i.e. leading to an unscheduled visit to a health care professional and diagnostic testing, either laboratory or imaging
	Minimal	Overt bleeding not meeting criteria above

BARC = Bleeding Academic Research Consortium, CABG = coronary artery by-pass grafting, Hb = haemoglobin, PLATO = platelet inhibition and patient outcomes, TIMI = thrombolysis in myocardial infarction

To summarise important results regarding the outcome bleedings, we defined three categories and ranked the scales to determine which results to use in the meta-analyses, in the following order:

- *Clinically significant bleeding*: (i) TIMI major + minor + requiring medical attention, (ii) BARC ≥2, (iii) PLATO major + minor, (iv) other defined scales: major + minor
- *Major bleeding*: (i) TIMI major, (ii) BARC ≥3, (iii) PLATO major, (iv) other definitions of major bleedings
- *Any bleeding*

We decided that summarising conclusions be provided only for the clearly defined bleeding outcomes clinically significant bleeding and major bleeding.

Clinically significant bleeding

A total of 8 RCTs including 25,407 patients reported results regarding clinically significant bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of clinically significant bleeding in the ticagrelor group ranged between 0% and 24%. The meta-analysis of all RCTs revealed an absolute risk difference of -1.9% (-3.6% to -0.2%) favouring clopidogrel (Figure 10). For all double- and single-blind RCTs included in this meta-analysis, the rate of clinically significant bleedings was statistically higher in the ticagrelor group (n=5, 24,789 patients; pooled absolute risk difference: -2.9%, (-4.7% to -1.1%).

The sensitivity analyses confirmed that a significant risk difference was consistent (Table 5). The funnel plot illustrated that publication bias cannot be fully excluded (Figure 11). When 1 RCT with at least one zero-event arm were excluded (contributing 1 (0.03%) out of a total of 3,162 events), the pooled absolute risk difference was -2.3% (-4.0% to -0.5%) (Appendix 6).

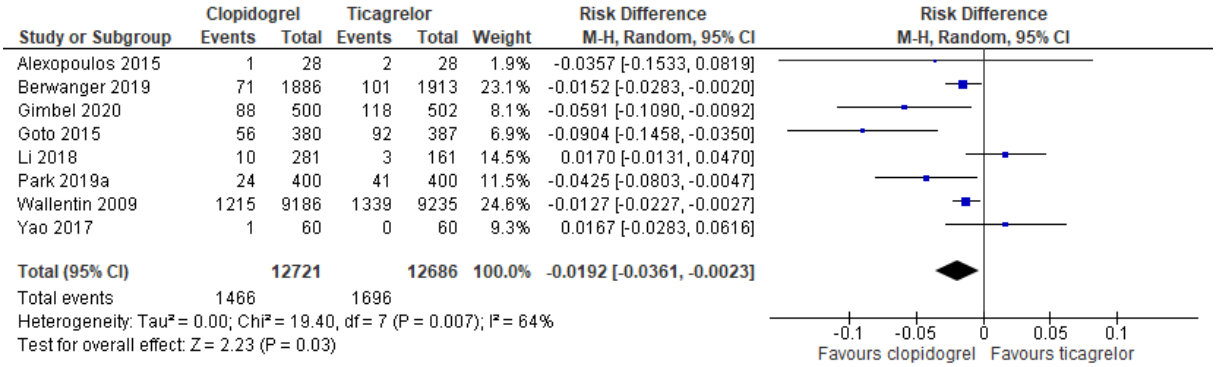


Figure 10 Forest plot and meta-analysis of RCTs providing results regarding clinically significant bleeding.

Table 5 Sensitivity analysis regarding clinically significant bleeding. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	8	25,407	**-1.9% (-3.6% to -0.2%)**
P	Including non-Asian patients	4	23,278	**-1.5% (-2.4% to -0.6%)**
I/C	Relevant dosage	7	25,351	**-1.9% (-3.7% to -0.2%)**
O	Recruited after PLATO	7	6,986	-2.5% (-5.5% to 0.4%)
	Follow-up 6-12 months	7	25,351	**-1.9% (-3.7% to -0.2%)**
Analysis	RR	8	25,407	**0.76 (0.64 to 0.91)**
	Only trials with ≥1 event in each randomisation group	7	25,287	**-2.3% (-4.0% to -0.5%)**
	Not major risk of bias	6	24,909	**-2.5% (-4.2% to -0.7%)**

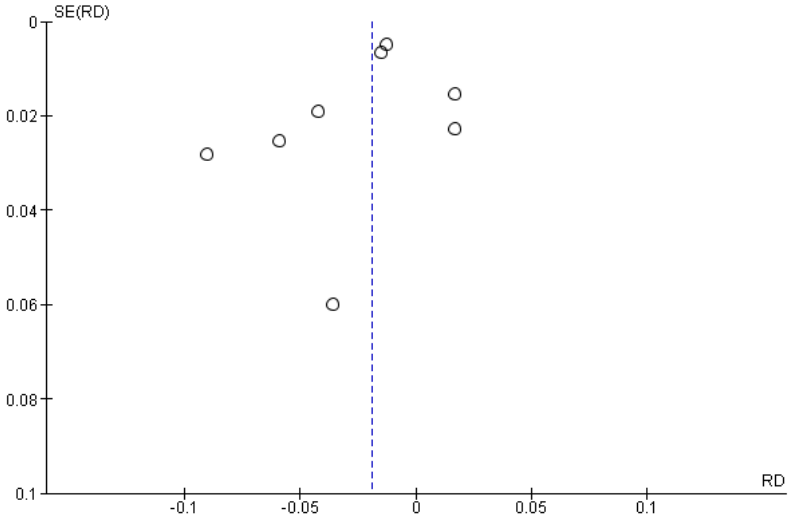


Figure 11 Funnel plot of RCTs providing results regarding clinically significant bleeding.

A total of 9 non-RCTs including 58,468 patients reported results regarding clinically significant bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 4 of these (35,738 patients) reported either adjusted hazard ratios regarding clinically significant bleeding or hazard ratios between matched groups, resulting in a pooled hazard ratio of 0.69 (0.49 to 0.96) favouring clopidogrel (Figure 12).

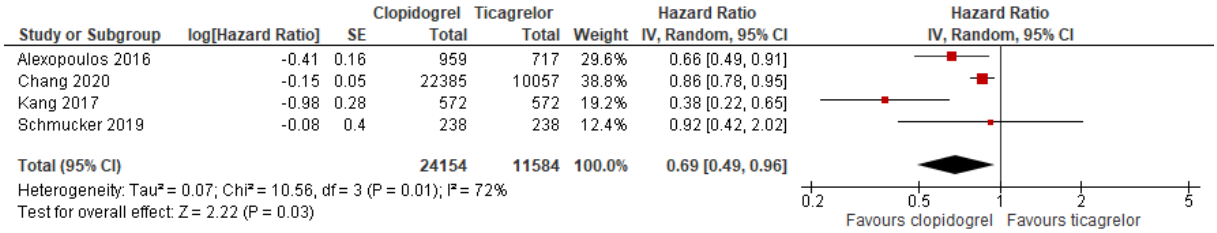


Figure 12 Forest plot and meta-analysis of non-RCTs providing poolable results regarding clinically significant bleeding.

In the GRADE process, we did not find reasons to downgrade the certainty of evidence. The results were consistent over the sensitivity analyses, although not reaching statistical significance when the PLATO trial was excluded. In the main forest plot of RCTs, Li et al., (2018) may give the impression of contrasting results. However, that trial randomised 324 patients to clopidogrel and 329 patients to ticagrelor and restricted the analysis to those who did not switch (n=282 versus n=161). With more than half of the patients in the ticagrelor group being excluded, we determined that this trial should not affect the conclusion. All large RCTs, either double-blind or single-blind with blinded outcome assessments, individually showed significant results favouring clopidogrel (Wallentin et al., 2009, Goto et al., 2015, Berwanger et al., 2019, Park et al., 2019a, Gimbel et al., 2020). To explore the potential influence of our ranking of bleeding scales, we performed a meta-analysis of the outcome PLATO major and minor bleeding, provided in the five RCTs just mentioned, with significant results favouring clopidogrel (RD: -3.2% (-5.5% to -1.0%). In this analysis, all but one RCT restricted to patients <75 years of age (Berwanger at el., 2019) individually showed a significant difference favouring clopidogrel.

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor results in a reduced risk of clinically significant bleedings (high certainty of evidence, GRADE ⊕⊕⊕⊕).*

Major bleedings

A total of 26 RCTs including 29,553 patients reported results regarding major bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of major bleeding in the ticagrelor group ranged between 0% and 10%. The meta-analysis of all RCTs regarding the absolute risk difference passed the line of unity: -0.2% (-0.6% to 0.2%) (Figure 13). Two RCTs with blinded adjudication of endpoints, showed significant results favouring clopidogrel (Park et al., 2019a, Gimbel et al., 2020). In the sensitivity analysis where risk ratio was analysed instead of risk difference, significant results favouring clopidogrel were shown (Table 5). The funnel plot illustrated that publication bias may not be a prominent problem (Figure 14). When 11 RCTs with at least one zero-event arm were excluded (contributing 6 (0.4%) out of a total of 1,618 events), the pooled absolute risk difference was -0.8% (-1.5% to -0.03%) (Appendix 6).

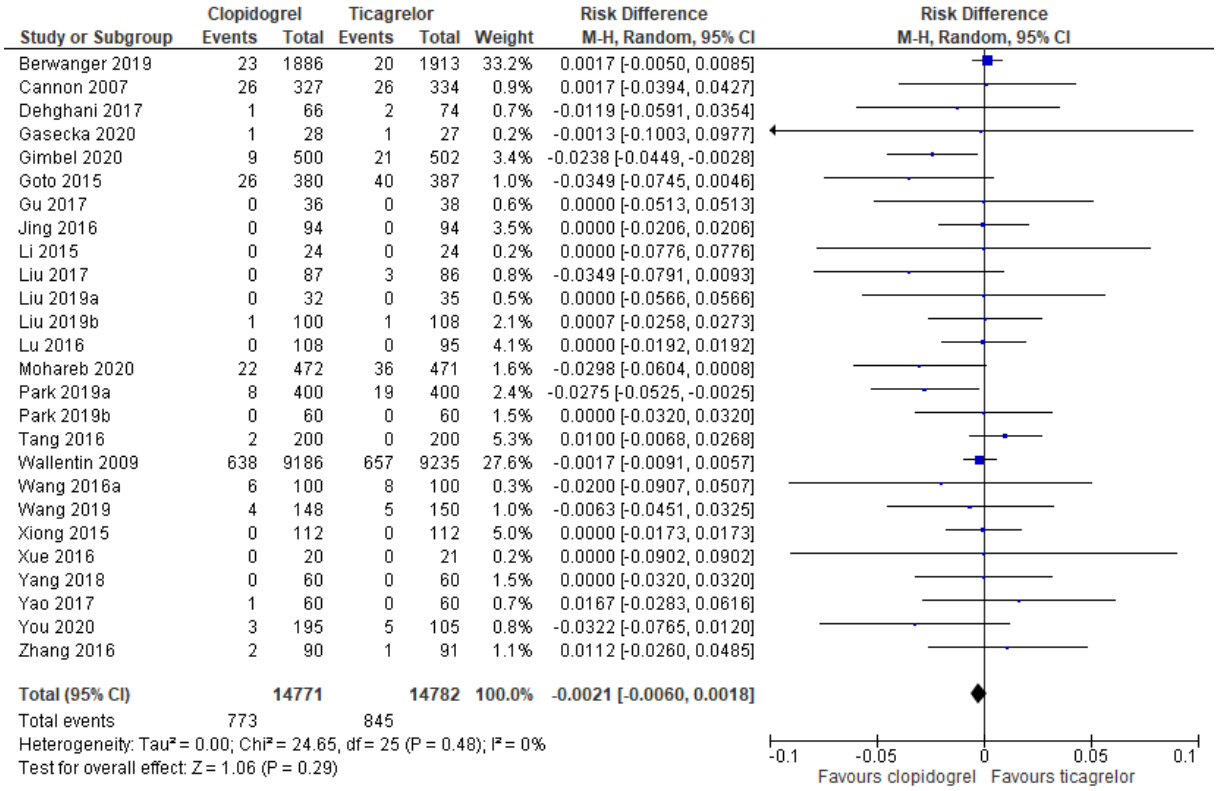


Figure 13 Forest plot and meta-analysis of RCTs providing results regarding major bleeding.

Table 6 Sensitivity analysis regarding major bleeding. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	26	29,553	-0.2% (-0.6% to 0.2%)
P	Including non-Asian patients	7	25,021	-0.5% (-1.3% to 0.3%)
I/C	Relevant dosage	21	28,959	-0.4 % (-1.0% to 0.1%)
O	Recruited after PLATO	24	10,471	-0.6% (-1.3% to 0.2%)
	Follow-up 6-12 months	18	27,985	-0.4% (-1.0% to 0.2%)
Analysis	RR	17	28,468	**0.80 (0.66 to 0.98)**
	Only trials with ≥1 event in each randomisation group	15	27,948	**-0.8% (-1.5% to -0.03%)**
	Not major risk of bias	17	28,310	-0.5% (-1.1% to 0.1%)

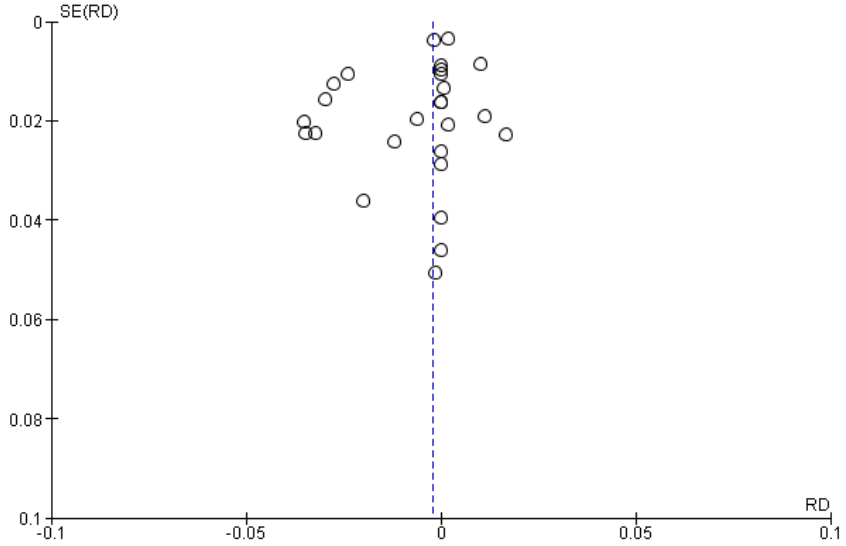


Figure 14 Funnel plot of RCTs providing results regarding major bleeding.

A total of 35 non-RCTs including 451,736 patients reported results regarding major bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 17 of these (306,180 patients) reported either adjusted hazard ratios regarding major bleeding or hazard ratios between matched groups, resulting in a pooled hazard ratio of 0.85 (0.76 to 0.95) favouring clopidogrel (Figure 15).

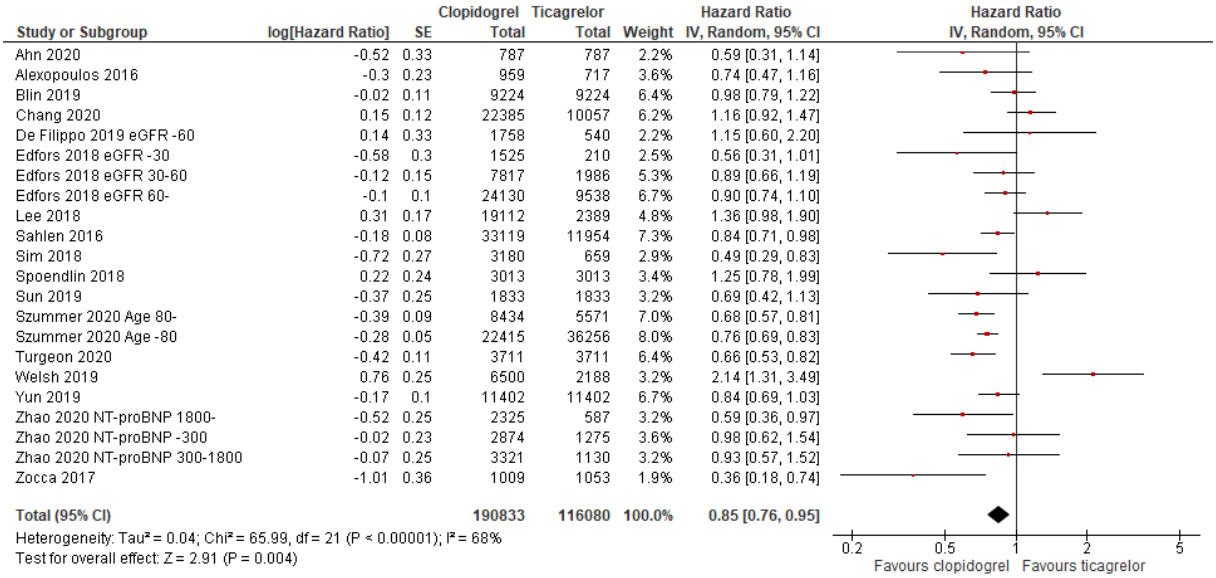


Figure 15 Forest plot and meta-analysis of non-RCTs providing poolable results regarding major bleeding.

In the GRADE process, we downgraded one step because of serious study limitations. The bias introduced in the meta-analysis by the handling of zero-event trials was substantial. GRADE was downgraded one additional step because of serious inconsistency; the sensitivity analyses did not confirm robustness of the results.

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of major bleeding, but shows a reduced risk of major bleeding when zero-event trials are excluded (low certainty of evidence, GRADE ⊕⊕◯◯).*

Any bleeding

A total of 15 RCTs including 7,150 patients reported results regarding any bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of any bleeding in the ticagrelor group ranged between 4.1% to 25%. The meta-analysis of all RCTs revealed an absolute risk difference of -3.0% (-5.1% to -0.9%) favouring clopidogrel (Figure 16).

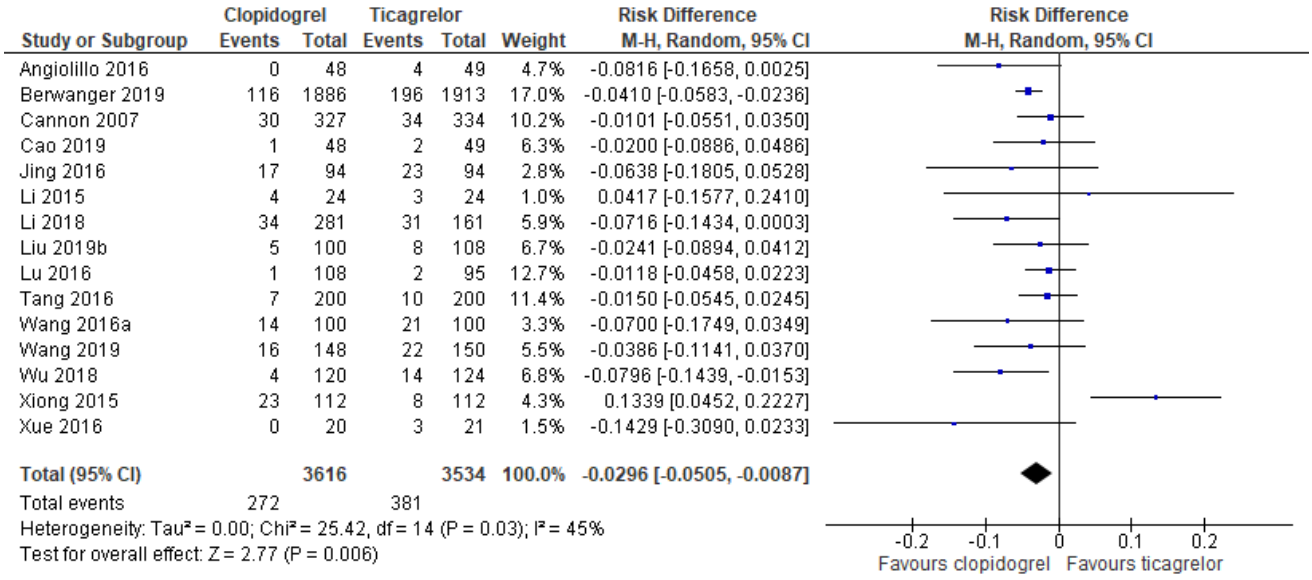


Figure 16 Forest plot and meta-analysis of RCTs providing results regarding any bleeding.

A total of 4 non-RCTs including 38,329 patients reported results regarding any bleeding in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 3 of these (35,992 patients) reported either adjusted hazard ratios regarding all-cause mortality or hazard ratios between matched groups, resulting in a pooled hazard ratio of 0.85 (0.76 to 0.95), favouring clopidogrel (Figure 17).

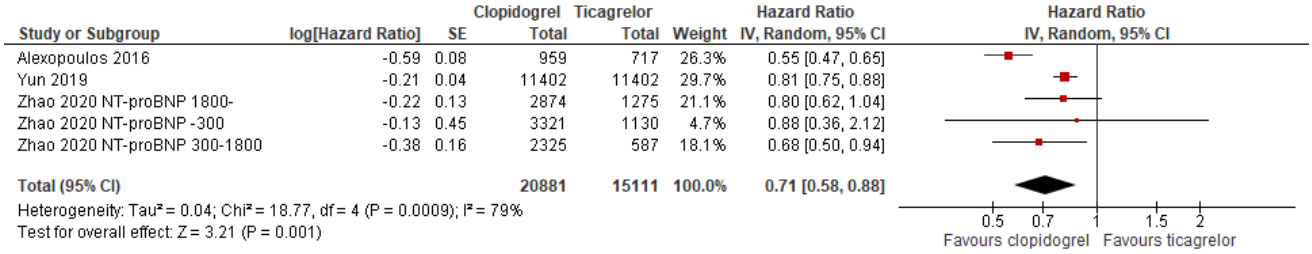


Figure 17 Forest plot and meta-analysis of non-RCTs providing poolable results regarding any bleeding.

Stent thrombosis (Appendix 4.4)

A total of 18 RCTs including 16,629 patients reported results regarding stent thrombosis in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of stent thrombosis in the ticagrelor group ranged between 0% and 1.3%. Six RCTs reported events of definite stent thrombosis (Cao et al., 2019, Gimbel et al., 2020, Park et al., 2019a, Park et al., 2019b, Wallentin et al., 2009, You et al., 2020), whereas the remaining studies reported events that were not as well defined. The meta-analysis of all RCTs revealed an absolute risk difference of 0.7% (0.4% to 1.1%) favouring ticagrelor (Figure 18), with significant differences in all sensitivity analyses (Table 6). The funnel plot illustrated that publication bias cannot be fully excluded (Figure 19). When 13 RCTs with at least one zero-event arm were excluded (contributing 23 (10%) out of a total of 225 events), the pooled absolute risk difference was 0.6% (0.02% to 1.0%) (Appendix 6).

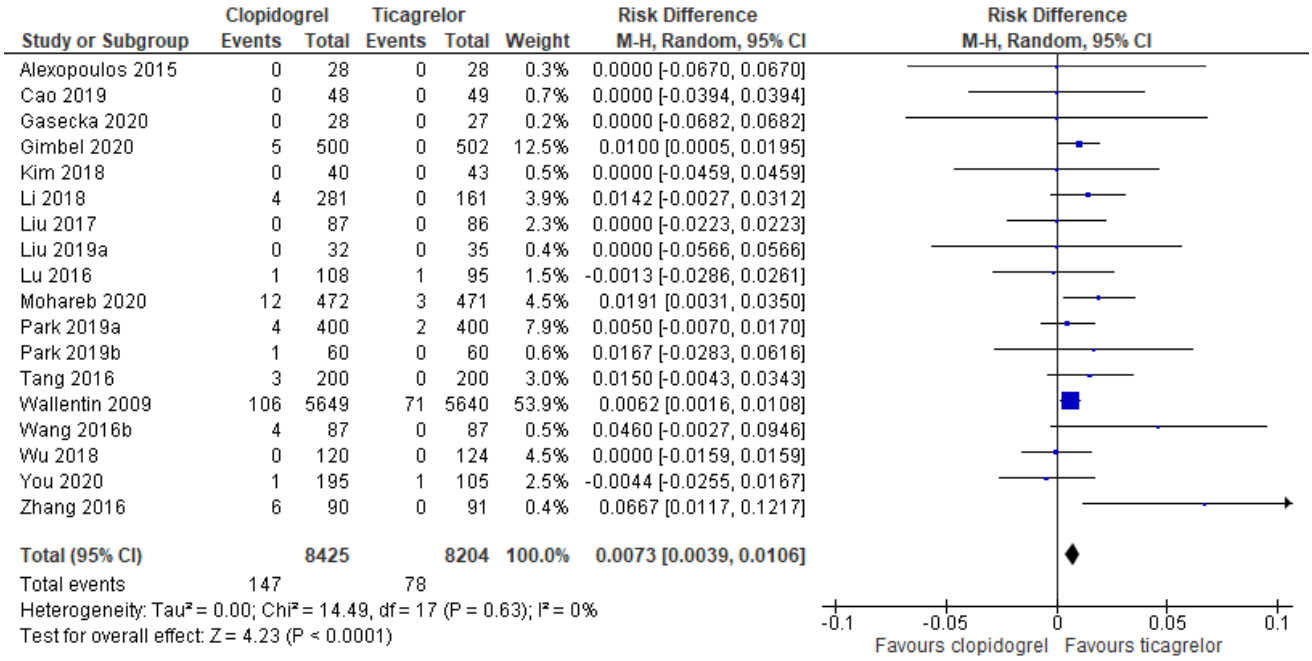


Figure 18 Forest plot and meta-analysis of RCTs providing results regarding stent thrombosis.

Table 6 Sensitivity analysis regarding stent thrombosis. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	18	16,629	**0.7% (0.4% to 1.1%)**
P	Including patients from non-Asian countries	5	13,345	**0.8% (0.5% to 1.2%)**
I/C	Dosing according to SPC	15	13,340	**0.7% (0.4% to 1.1%)**
O	Recruited after PLATO	17	5,372	**0.9% (0.4% to 1.3%)**
	Follow-up 6-12 months	12	15,979	**0.8% (0.4% to 1.1%)**
Analysis	RR	11	15,854	**1.75 (1.28 to 2.39)**
	Only trials with ≥1 event in each randomisation group	5	13,535	**0.6% (0.02% to 1.0%)**
	Not major risk of bias	11	22,647	**0.7% (0.3% to 1.0%)**
RCTs restricted to those particularly relevant to this HTA	Dosing according to SPC Recruited after PLATO No outlier populations* Only trials with ≥1 event in each randomisation group	4	2,246	0.7% (-0.4% to 1.7%)

*Outlier populations observed in the funnel plot (Figure 19), found to have a feature in common that diverge from all other studies: event rate >4% in the clopidogrel group.

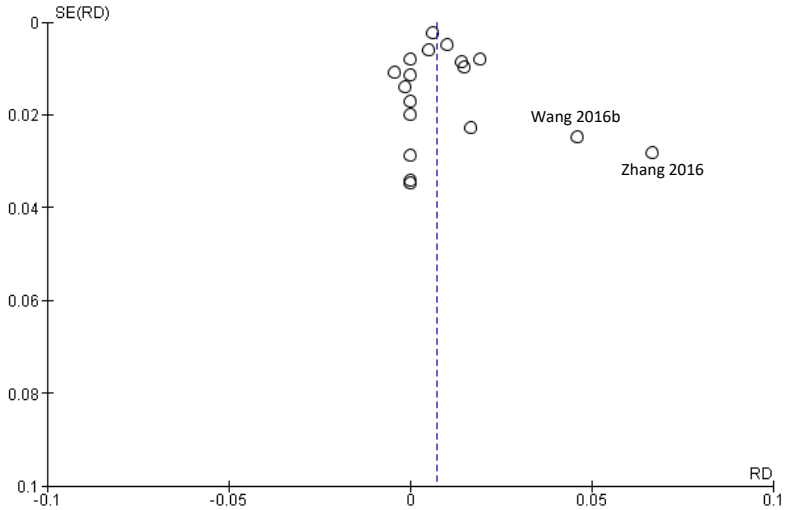


Figure 19 Funnel plot of RCTs providing results regarding stent thrombosis.

A total of 17 non-RCTs including 82,030 patients reported results regarding stent thrombosis in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In all, 5 non-RCTs (22,852 patients) reported either adjusted hazard ratios regarding stent thrombosis or hazard ratios between matched groups, resulting in a pooled hazard ratio of 0.94 (0.59 to 1.51) (Figure 20).

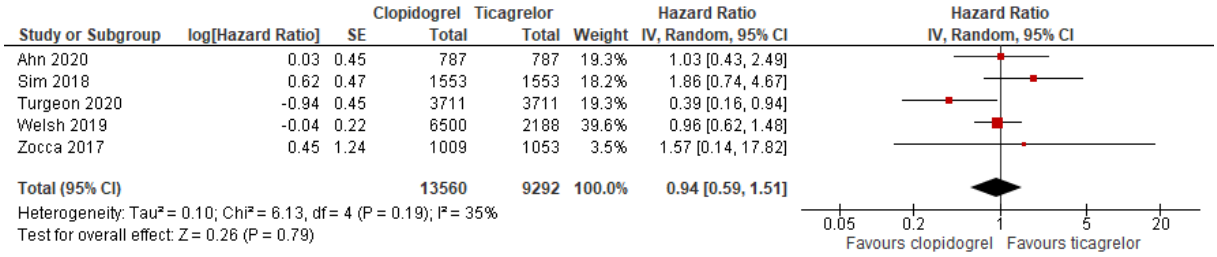


Figure 20 Forest plot and meta-analysis of non-RCTs providing poolable results regarding stent thrombosis.

In the GRADE process, we downgraded one step because of the serious indirectness. All studies contributing to the meta-analysis had directness issues. For instance, the rate of definite stent thrombosis in the PLATO trial was 1.9% in the clopidogrel group and 1.3% in the ticagrelor group (Wallentin et al., 2009). These rates are higher than the rate in Region Västra Götaland, being 0.7% for patients undergoing PCI in 2005 to 2015 (Völz et al., 2020).

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor is probably slightly less efficient in reducing the risk of stent thrombosis (moderate certainty of evidence, GRADE ⊕⊕⊕◯).*

Angina (Appendix 4.5)

A total of 5 RCTs including 1,109 patients reported results regarding angina in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. We did not consider the outcomes provided in one RCT, hospitalisation for angina, sufficiently similar to be included in the meta-analysis (Li et al., 2018). Indeed, angina implies subjective symptoms that often do not require hospitalisation since instant intake of glyceryl trinitrate suffices for relief. In the four RCTs that were pooled, the rate of angina in the ticagrelor group ranged between 0% and 8.3%. The meta-analysis of these RCTs revealed an absolute risk difference of 6.5% (2.9% to 10%) favouring ticagrelor (Figure 21).

No non-RCTs provided results regarding angina.

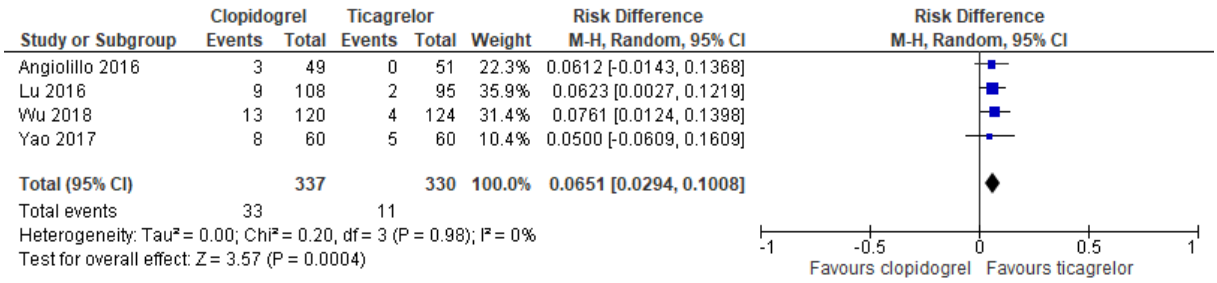


Figure 21 Forest plot and meta-analysis of RCTs providing results regarding angina.

In the GRADE process, we downgraded one step because of serious study limitations. All RCTs were open-label, a design that is problematic as angina is a subjective outcome. In addition, angina was not clearly defined in the studies. The certainty of evidence was downgraded one additional step because of serious indirectness regarding patient population or setting.

Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may be less efficient to reduce angina
(low certainty of evidence, GRADE ⊕⊕◯◯).

Rehospitalisation (Appendix 4.6)

A total of 5 RCTs including 831 patients reported results regarding rehospitalisation in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. We considered the results provided by Li et al. (2018), rehospitalisation for angina, too restricted to be included in the meta-analysis. In the 4 RCTs that were pooled in a meta-analysis, the rate of rehospitalisation in the ticagrelor group ranged between 2.7% and 5.3%. The pooled absolute risk difference was 3.4% (-0.9% to 7.8%) passing the line of unity (Figure 22),

No non-RCTs provided results regarding rehospitalisation.

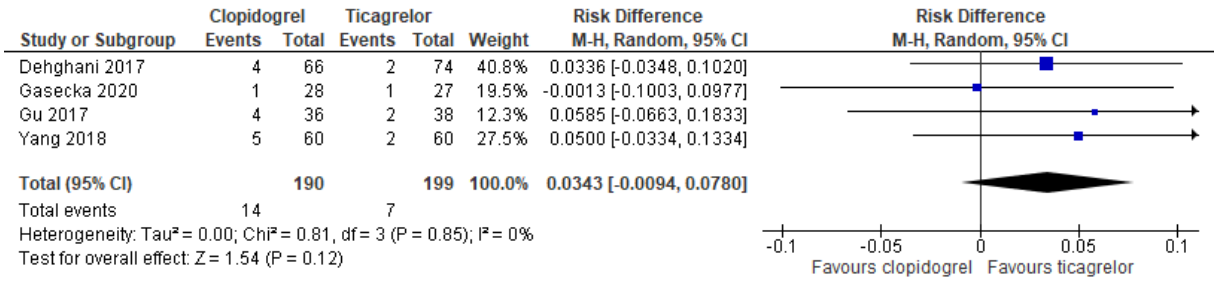


Figure 22 Forest plot and meta-analysis of RCTs providing results regarding rehospitalisation.

In the GRADE process, we downgraded one steps because of serious study limitations. Two RCTs were designed to evaluate platelet function (Dehghani et al., 2017) and extracellular vesicle concentrations (Gasecka et al., 2020), and the others had major risk of bias. We also downgraded one step because of serious indirectness regarding patient population or setting. Finally, we downgraded one step because of serious imprecision, with few patients and few events included in the meta-analysis.

Conclusion: In ACS patients subjected to DAPT, it is uncertain whether use of clopidogrel compared with ticagrelor affects the risk of rehospitalisation
(very low certainty of evidence, GRADE ⊕◯◯◯).

Health-related quality of life (Appendix 4.7)

One publication, including 15,212 patients from the PLATO trial, reported results regarding HRQL in ACS patients treated with clopidogrel or ticagrelor, combined with ASA (Levin et al., 2013). No between-group differences were found in EuroQol 5 dimensions (EQ-5D): 0.863 vs 0.864, P=0.69 after twelve months.

One non-RCT, including 1,083 patients and serious study limitations, reported results regarding HRQL in ACS patients treated with clopidogrel or ticagrelor, combined with ASA.

In the GRADE process, we downgraded one step because of serious study limitations. The HRQL instrument used in the RCT does not capture adverse reactions associated with the study treatment. We also downgraded one step because of serious imprecision. More than 75% of the patients in the RCT had no problems according to all dimensions in EQ-5D already at discharge, diminishing the potential to find potential differences. Finally, we downgraded one step because of some indirectness and some inconsistency; only one RCT, with indirectness issues, contributed data.

Conclusion: In ACS patients subjected to DAPT, it is uncertain whether use of clopidogrel compared with ticagrelor affects HRQL (very low certainty of evidence, GRADE ⊕◯◯◯).

Dyspnea (Appendix 4.8)

A total of 17 RCTs including 25,934 patients reported results regarding dyspnea in ACS patients treated with clopidogrel or ticagrelor, combined with ASA. Two RCTs reported only the rate of dyspnea as the reason for premature discontinuation (Park et al., 2019a, Park et al., 2019b). We considered these outcomes too restricted to be included in the meta-analyses. In the 15 RCTs that were pooled, the rate of dyspnea in the ticagrelor group ranged between 2.4% and 24%. The meta-analysis of these RCTs revealed an absolute risk difference of -6.0% (-7.8% to -4.2%) favouring clopidogrel (Figure 23), the sensitivity analyses revealing that this risk difference was consistent (Table 7). The funnel plot illustrated that publication bias cannot be fully excluded (Figure 24). When 7 RCTs with at least one zero-event arm were excluded (contributing 26 (0.9%) out of a total of 2,870 events), the pooled absolute risk difference was -6.0% (-8.3% to -3.9%) (Appendix 6).

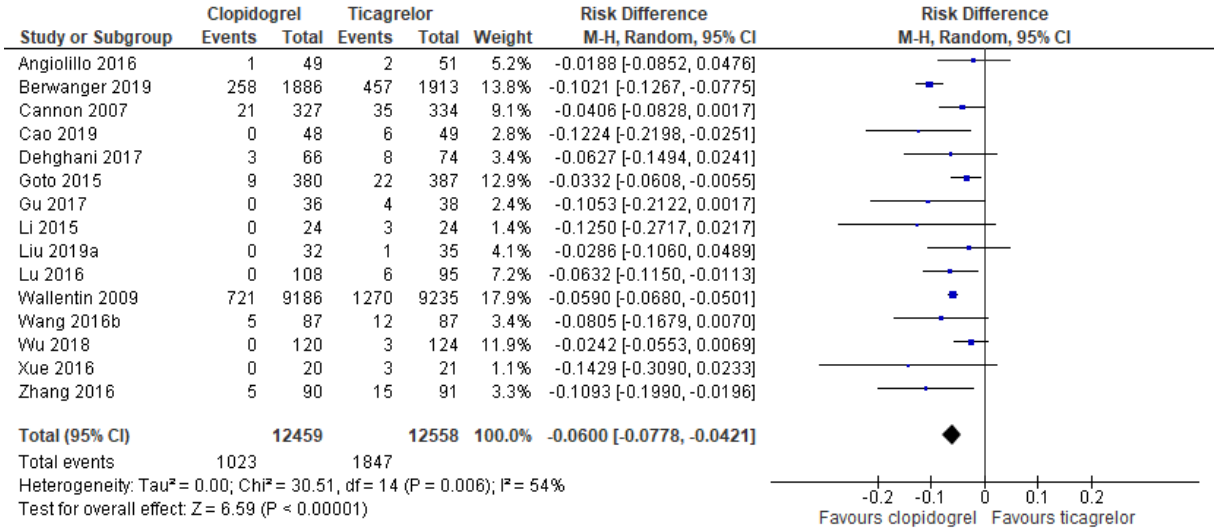


Figure 23 Forest plot and meta-analysis of RCTs providing results regarding dyspnea.

Table 7 Sensitivity analysis regarding dyspnea. Results not including the line of unity are bolded.

		RCTs (n)	Patients (n)	RD/RR (95% CI)
All	No restrictions	15	25,017	**-6.0% (-7.8% to -4.2%)**
P	Including non-Asian patients	5	23,118	**-6.3% (-9.1% to -3.5%)**
I/C	Relevant dosage	11	24,644	**-5.8% (-7.7% to -3.8%)**
O	Recruited after PLATO	14	6,596	**-6.4% (-9.0% to -3.7%)**
	Follow-up 6-12 months	7	23,663	**-6.2% (-8.6% to -3.7%)**
Analysis	RR	15	25,017	**0.56 (0.52 to 0.61)**
	Only trials with ≥1 event in each randomisation group	8	24,240	**-6.0% (-8.3% to -3.9%)**
	Not major risk of bias	8	24,332	**-5.3% (-7.4% to -3.2%)**

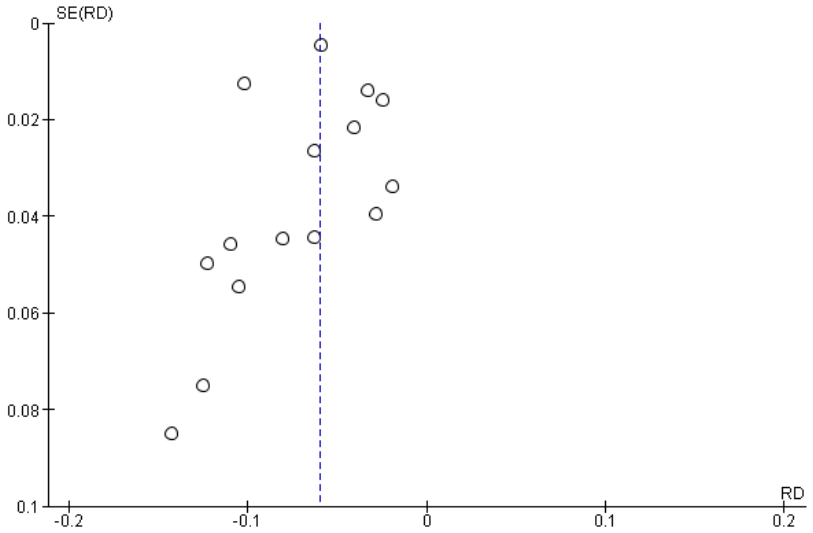


Figure 24 Funnel plot of RCTs providing results regarding dyspnea.

In all, one non-RCT including 7,422 patients reported results regarding dyspnea in ACS patients treated with clopidogrel or ticagrelor, with a hazard ratio of 0.41 (0.29 to 0.59) (Turgeon et al., 2020).

In the GRADE process, we did not find reasons to downgrade the certainty of evidence. Although the funnel plot suggests that some publication bias cannot be excluded, the results were consistent over all sensitivity analyses. Further, the two double-blind RCTs showed significant results favouring clopidogrel (Wallentin et al., 2009, Goto et al., 2015), and the analyses with/without zero-event studies showed similar results.

> *Conclusion: In ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor results in a reduced risk of dyspnea*
> *(high certainty of evidence, GRADE ⊕⊕⊕⊕).*

P2: Older patients

Two RCTs and two non-RCTs, described in Table 8, contributed to the evidence base regarding the use of clopidogrel or ticagrelor in older ACS patients subjected to DAPT.

Table 8 Characteristics of studies contributing to the evidence base in P2.

		Current patients[1]	Gimbel et al., 2020	Wang et al., 2016a	Szummer et al., 2020	Schmucker et al., 2019
Country		Sweden	Netherlands	China	Sweden	Germany
Design		N/A	RCT	RCT	Non-RCT	Non-RCT
Recruitment		N/A	2013-2018	2013-2014	2010-2017	2006-2017
Patients	In analysis (n)	N/A	1,002	200	14,005	1,087/476[7]
	STEMI/NSTEMI/UAP (%)[2]	26/49/25[3]	0/86/11	34/46/20	31/69/0	100/0/0
Age (years)	Mean/median	67	77	79	85	81
	75+	30%[4]	65% (all ≥70)	NR (all ≥65)	100% (all ≥80)	100% (all ≥75)
PCI		90%	47%	73%	58%	100%
	DES[5]	100%	93%	NR	NR	38%

[1]according to SCAAR.
[2]diagnosis at discharge, does not always add up to 100% because another diagnosis was recorded at discharge.
[3]National data.
[4]Regional data; Völz et al., (2020).
[5]Percentage of those with PCI.

P2, results per outcome

Mortality (Appendix 4.1)

All-cause mortality

A total of two RCTs including 1,202 patients reported results regarding all-cause mortality in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of all-cause mortality in the ticagrelor group was 6.8% and 9%. The meta-analysis of both RCTs passed the line of unity (Figure 24).

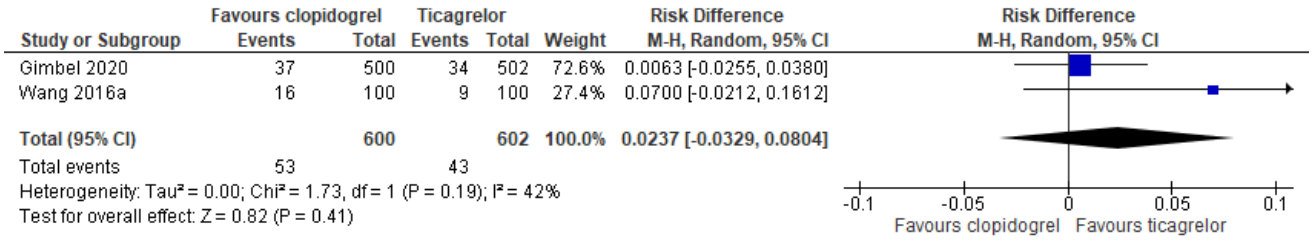


Figure 24 Forest plot and meta-analysis of RCTs providing results regarding all-cause mortality in older ACS patients subjected to DAPT.

A total of two non-RCTs including 14,481 patients reported results regarding all-cause mortality in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA. Both reported results that could be pooled, resulting in a hazard ratio of 0.92 (0.72 to 1.19) (Figure 25).

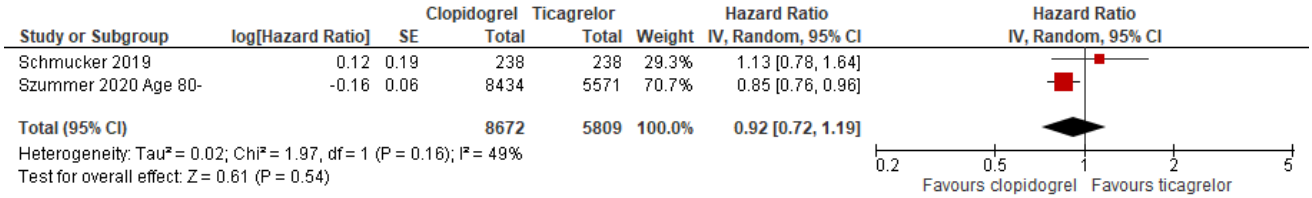


Figure 25 Forest plot and meta-analysis of non-RCTs providing results regarding all-cause mortality in older patients subjected to DAPT.

The RCT by Wang et al. (2016a) was an outlier (Figure 2), with an all-cause mortality rate being higher than can be expected in older ACS patients in general. In addition, that trial provided sparse information for assessments of directness and study limitations (Appendix 5). Therefore, the GRADE assessments were primarily based on the RCT by Gimbel et al. (2020). In the GRADE process, we downgraded one step because of serious imprecision; with 71 events, the confidence interval was wide. We also downgraded one step because of the combination of some study limitations and some indirectness. In the trial, which was open-label for patients and treating physicians, 22% discontinued clopidogrel and 47% discontinued ticagrelor, and it cannot be excluded that this may have biased the results as discontinuations may result from bleeding complications. Regarding directness, patients with STEMI were not included. We did not downgrade for consistency as the RCT that formed the primary basis for the conclusion was a multi-centre trial performed in 12 sites. The uncertainty was therefore not considered sufficient for downgrading.

> *Conclusion: In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of all-cause mortality (low certainty of evidence, GRADE ⊕⊕◯◯).*

CV mortality

A total of two RCTs including 1,202 patients reported results regarding CV mortality in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of CV mortality in the ticagrelor group was 3.0% and 6%. The meta-analysis of both RCTs passed the line of unity (Figure 26).

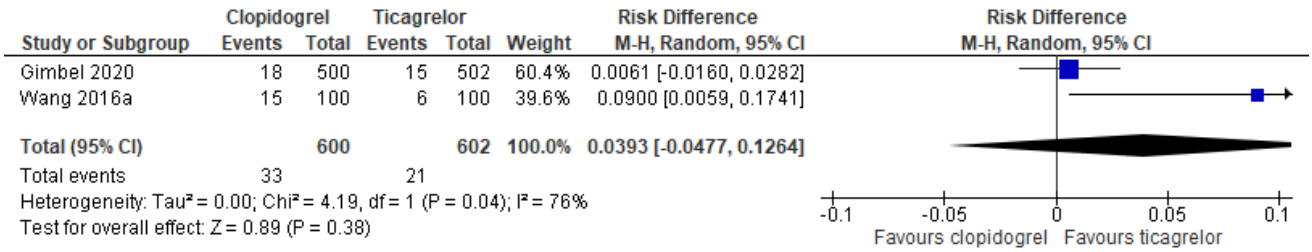


Figure 26 Forest plot and meta-analysis of RCTs providing results regarding CV mortality in older ACS patients subjected to DAPT.

No non-RCTs provided results regarding CV mortality in P2.

For the same reasons as for all-cause mortality, the GRADE assessments regarding CV mortality were primarily based on the RCT by Gimbel et al. (2020). In the GRADE process, we downgraded one step because of serious imprecision; with 33 events, the confidence interval was wide. We also downgraded one step because of the combination of some study limitations and some indirectness and did not downgrade for consistency, as described for all-cause mortality.

Conclusion: In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of CV mortality (low certainty of evidence, GRADE ⊕⊕◯◯).

Myocardial infarction (Appendix 4.2)

A total of two RCTs including 1,202 patients reported results regarding MI in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA. In these trials, the rate of all-cause mortality in the ticagrelor group was 7.4% and 6%. The meta-analysis of both RCTs passed the line of unity (Figure 27).

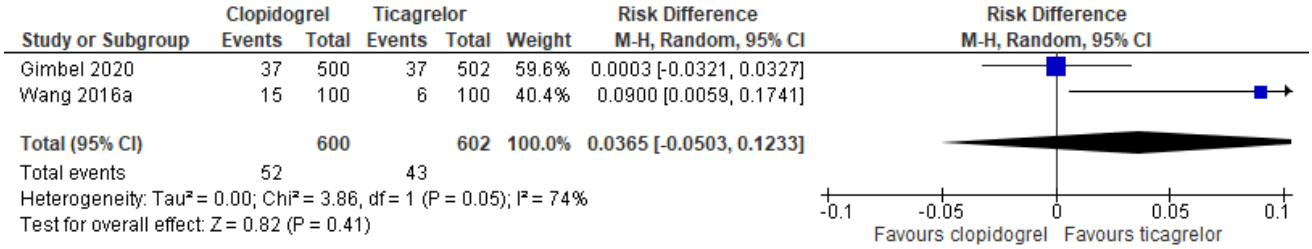


Figure 27 Forest plot and meta-analysis of RCTs providing results regarding MI in older ACS patients subjected to DAPT.

In all, one non-RCT including 14,005 patients reported results regarding MI in older ACS patients treated with clopidogrel or ticagrelor, with a hazard ratio of 1.25 (1.09 to 1.43) (Szummer et al., 2020).

For the same reasons as for all-cause mortality, the GRADE assessments regarding MI were primarily based on the RCT by Gimbel et al. (2020). In the GRADE process, we downgraded one step because of serious imprecision; with 74 events, the confidence interval was wide.
We also downgraded one step because of the combination of some study limitations and some indirectness and did not downgrade for consistency, as described for all-cause mortality.

Conclusion: In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor may result in little or no difference in the risk of MI (low certainty of evidence, GRADE ⊕⊕◯◯).

Bleeding (Appendix 4.3)

Clinically significant bleeding

One RCT, including 1,002 patients, reported results regarding clinically significant bleeding in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA (Gimbel et al., 2020). This trial was designed with a primary aim to evaluate clinically significant bleedings in older NSTE-ACS patients The rate of such bleedings was 18% in the clopidogrel group and 24% in the ticagrelor group, resulting in a hazard ratio of 0.71 (0.54 to 0.94) favouring clopidogrel. The absolute risk difference was -5.9% (-11% to -0.9%).

One non-RCT, including 474 patients in a propensity score-matched analysis, reported results regarding clinically significant in older ACS patients treated with clopidogrel or ticagrelor, with a hazard ratio of 0.93 (0.42 to 2.04) (Schmucker et al., 2019).

In the GRADE process, we downgraded one step because of some uncertainty regarding consistency (only one trial) and some imprecision. Only one RCT contributed data. This trial had single-blind adjudication of the events by an assessment committee masked to treatment allocation and showed significant results regarding the primary aim to evaluate clinically significant bleeding,

Conclusion: In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor probably results in a substantially reduced risk of clinically significant bleeding (moderate certainty of evidence, GRADE ⊕⊕⊕◯).

Major bleeding

A total of two RCTs, including 1,202 patients, reported results regarding major bleeding in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA. The rate of major bleeding was 4.2% and 8% in the ticagrelor group. The pooled absolute risk difference was -2.4% (-4.4% to -0.3%) favouring clopidogrel (Figure 27),

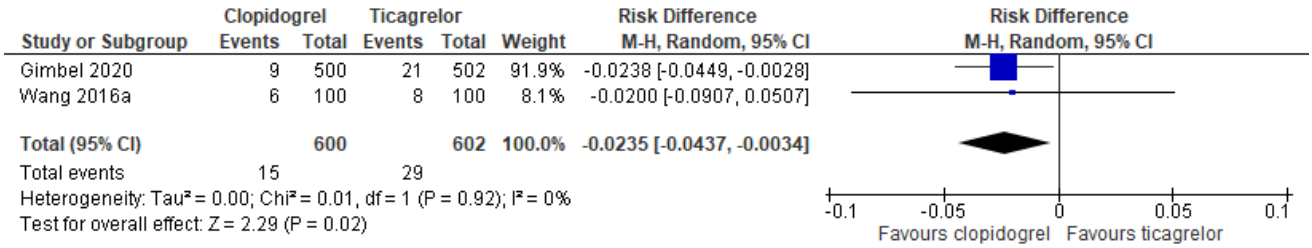


Figure 27 Forest plot and meta-analysis of RCTs providing results regarding major bleeding in older ACS patients subjected to DAPT.

In all, one non-RCT including 14,005 patients reported results regarding major bleeding in older ACS patients treated with clopidogrel or ticagrelor, with a hazard ratio of 0.68 (0.57 to 0.80) (Szummer et al., 2020).

In the GRADE process, we downgraded one step because of some imprecision.

Conclusion: In older ACS patients subjected to DAPT, use of clopidogrel compared with ticagrelor probably results in a reduced risk of major bleeding (moderate certainty of evidence, GRADE ⊕⊕⊕◯).

Stent thrombosis (Appendix 4.4)

One RCT, including 1,002 patients, reported results regarding stent thrombosis in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA (Gimbel et al., 2020). Five events were reported in the clopidogrel group and none in the ticagrelor group.

No non-RCTs provided results regarding stent thrombosis in P2.

In the GRADE process, we downgraded one step because of the serious study limitations. As definite stent thrombosis requires verification with angiography, detection bias cannot be fully excluded in an open-label RCT; the treating physician may primarily suspect stent thrombosis in those assigned to the clopidogrel group, and consequently perform angiography to a smaller extent in the ticagrelor group. Further, the uneven discontinuation rates were considered problematic, as described for all-cause mortality. We also downgraded one step because of serious imprecision, with only 5 events available. Finally, we downgraded one step because of some indirectness as patients with STEMI were not included.

Conclusion: In older ACS patients subjected to DAPT, it is uncertain whether use of clopidogrel compared with ticagrelor affects the risk of stent thrombosis (very low certainty of evidence, GRADE ⊕◯◯◯).

Angina (Appendix 4.5)

No RCT and no non-RCT provided results regarding angina in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA.

Rehospitalisation (Appendix 4.6)

No RCT and no non-RCT provided results regarding rehospitalisation in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA.

Health-related quality of life (Appendix 4.7)

No RCT and no non-RCT provided results regarding HRQL in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA.

Dyspnea (Appendix 4.8)

No RCT and no non-RCT provided results regarding dyspnea in older ACS patients treated with clopidogrel or ticagrelor, combined with ASA.

10. Organisational aspects

Time frame for the putative introduction of the new health technology

Both clopidogrel and ticagrelor are part of standard care for patients subjected to DAPT in ACS.

Present use of the technology in other hospitals in Region Västra Götaland

The current proportions of use of clopidogrel and ticagrelor in patients subjected to DAPT in ACS are approximately 20% and 80%, respectively. Clopidogrel is chosen for those concurrently treated with a direct-acting oral anticoagulant or warfarin, a situation in which there is no clear recommendation regarding DAPT.

Consequences of the new health technology for personnel

An increased use of clopidogrel would require a change in the regional guidelines, but would not require any specific technical or long-term personnel resources. Both DAPT alternatives are well-known to all personnel working in cardiology departments. As switching between different P2Y12 inhibitors is a complicated process, involving an increased risk of adverse events (Angiolillo et al., 2017), those already prescribed ticagrelor as part of their DAPT will probably not be switched following a potential change in regional guidelines. Instead, a potential changed prescribing recommendation is likely only to affect new patients subjected to DAPT. If a larger proportion of patients would be prescribed clopidogrel as part of DAPT, the need of health care consultancies for switching may be reduced as there will be less adverse reactions.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

In the regional guidelines, clopidogrel and ticagrelor are both recommended. However, many cardiologists adhere to the European guidelines, in which ticagrelor is preferred over clopidogrel. If the recommendations regarding DAPT would be revised, there would be a need for updating clinical recommendations and information to health care personnel. In that case, efforts to harmonise the recommendations in the region and in Sweden could be required.

11. Economic aspects

Present costs of currently used technology: ticagrelor

The present costs of ticagrelor (costs of ASA not included since these are the same in the comparison groups) is about 21 Swedish krona (SEK) per day and patient. The annual cost is approximately 7,700 SEK per patient.

Expected costs of the health technology at issue: clopidogrel

The costs of clopidogrel is about 1 SEK per day and patient. The annual cost is approximately 365 SEK per patient.

Total change in costs

The difference between the costs of clopidogrel and ticagrelor is -7,335 SEK per patient and year.

Given current treatment practice, with approximately 20% prescribed clopidogrel and 80% prescribed ticagrelor, the total annual costs in Region Västra Götaland amount to about 17.2 million SEK.

If the distribution between the treatment alternatives would change to 50% clopidogrel and 50% ticagrelor, the total annual costs would be reduced to approximately 11.1 million SEK, that is, a cost saving of about 6.1 million SEK compared with current practice.

If the distribution between the treatment alternatives would change to 80% clopidogrel and 20% ticagrelor, the total annual costs would be reduced to approximately 5.1 million SEK, that is, a cost saving of about 12.1 million SEK compared with current practice.

Possibility to adopt and use the new technology within the present budget

To use clopidogrel, instead of ticagrelor, in more patients subjected to DAPT in ACS would be possible within the present budget and would lead to cost savings as reported above. These resources could be used for other health care services within the area/clinic.

Available economic evaluations or cost advantages/disadvantages

There are numerous published economic evaluations and budget impact analyses comparing clopidogrel and ticagrelor for patients with ACS. A total of 46 studies containing economic analysis were identified in the searches. Focusing on studies within the Swedish health care setting, Henriksson et al. (2014) as well as Janzon et al. (2015) used data from the PLATO trial in addition to a long-term Markov model extrapolating long-term cardiovascular risks after the 12-month follow-up. In both studies, the estimated cost per gained quality adjusted life-year (QALY) with ticagrelor compared to clopidogrel was about SEK 25,000, which is substantially below the median cost per QALY for reimbursed drugs in Sweden, reported to be 350,000 (Svensson et al., 2015). The results were primarily driven by the gains in mortality and non-fatal MI found in the PLATO population, as well as the finding that there were more visits and other non-drug related health care costs for patients randomised to the clopidogrel group. As this HTA shows that the PLATO results are not fully applicable in current clinical practice, prior estimates of the cost per QALY may not be valid in the entire ACS population.

12. Ethical aspects

The compiled evidence regarding benefits and risks of clopidogrel or ticagrelor in ACS patients subjected to DAPT was not altogether concordant in all and in older patients. In all ACS patients, ticagrelor probably results in a slightly reduced risk of MI and stent thrombosis, but these beneficial effects were not evident in older patients. Regarding adverse effects, clopidogrel results in a reduced risk of clinically significant bleeding and dyspnea in ACS patients overall. In older patients, a substantially reduced risk of clinically significant bleeding can probably be expected, along with a probable reduced risk of major bleeding. Regarding mortality for ACS patients overall, clopidogrel may be associated with a slightly increased risk or imply little/no difference, whereas available evidence suggests little or no difference in older people. Given this benefit-risk profile of clopidogrel compared with ticagrelor, one can discuss the ethical aspect that the principle not to harm weighs heavier than the principle to do good. In addition, given this evidence base, it may be relevant to consider age in the choice of treatment. Furthermore, the principle of autonomy is relevant since perceptions about risks differ between patients. Indeed, both the perceived risk of future events and the attitude to harms of drug treatment vary between individuals.

Regarding the compatibility with other ethical values, equality and justice may be minor issues in most cases as far as the interventions evaluated in this HTA are concerned. Nevertheless, the Swedish reimbursement system implies that each individual has to pay a maximum of 2,350 SEK per year for drugs within the system.
As the drug costs, over the one-year treatment, is 7,700 SEK for ticagrelor and 365 SEK for clopidogrel, it cannot be excluded that choice of drug may be affected by income, in particular for patients who have not reached the threshold of 2,350 SEK and therefore have to pay themselves.

In summary, costs aspects not considered, this ethical analysis reveals that individualised treatment is a key issue for the choice between clopidogrel and ticagrelor, where the patient's perceptions regarding risks of future CV events need to be weighed against his/her perceptions regarding risks of adverse reactions including bleedings and dyspnea.

13. Discussion

Summary of main results

Overall, this HTA shows a slight benefit of ticagrelor over clopidogrel regarding outcomes reflecting the intended benefits of treatment (MI, stent thrombosis). Regarding adverse effects, on the other hand, use of clopidogrel is favourable, with reduced risks of clinically significant bleeding and dyspnea. Regarding the key outcome reflecting the net effect of this drug treatment (all-cause mortality) and CV mortality, the results are more uncertain; depending on the inclusion/exclusion of zero-event trials clopidogrel may either be slightly less efficient or there may be little or no difference. In the sensitivity meta-analysis including only selected RCTs of particular interest for this HTA, i.e. trials without off-label dosing investigating current relevant populations, no differences between clopidogrel and ticagrelor regarding all-cause and CV mortality were seen. For major bleeding, depending on the inclusion/exclusion of zero-event trials, there may be little or no difference between the compared treatment alternatives or clopidogrel may be associated with a reduced risk. In the sensitivity meta-analysis including selected RCTs, described above, a lower risk of major bleeding was seen for clopidogrel.

The overall findings, in all ACS patients subjected to DAPT regarding the comparison clopidogrel versus ticagrelor, differ somewhat from those found in older patients subjected to DAPT; beneficial effects of ticagrelor may not be found in the latter age group, and clopidogrel probably implies a substantially reduced risk of clinically significant bleeding and, also, a reduced risk of major bleeding. The RCT that formed the primary basis for the conclusions in older patients included participants 70 years or older in current European health care. The results in that trial, reflected in the conclusions of this HTA, seem to diverge from those of a subanalysis of PLATO where adjusted results were similar in older and younger patients for most outcomes (Husted et al., 2012). However, to remember, this is a subanalysis where the original randomisation no longer can be counted on.

On average, without considering characteristics of the patient or the other ACS treatment provided, and without taking the 95% CI into account, 125 and 143/167 (depending on handling of zero-event trials) ACS patients would probably need to be treated with ticagrelor to avoid one MI and one stent thrombosis, respectively. Correspondingly, 53/43 ACS patients would, on average, need to be treated with clopidogrel to avoid one clinically significant bleeding and one major bleeding, respectively. Furthermore, 17 ACS patients would, on average, need to be treated with clopidogrel to avoid one case of dyspnea. At older ages, where there is little or no beneficial effects of ticagrelor compared with clopidogrel according to available evidence, 17 and 42 ACS patients would probably, on average, need to be treated with clopidogrel to avoid one clinically significant bleeding and one major bleeding, respectively.

Compared with the PLATO trial, PCI is now used to a larger extent and the PCI process has improved, for instance with the routine use of DES. A conspicuous difference is that of the prevalence of stent thrombosis. In the PLATO trial, 1.9% of those assigned to the clopidogrel group had a definite stent thrombosis (Wallentin et al., 2009), whereas the corresponding figure for those treated with clopidogrel in Region Västra Götaland today, despite their being considerably older, is 0.7% (Völz et al., 2020). The low risk of stent thrombosis could impact the benefit-risk balance regarding the choice of antiplatelet drug. Interestingly, patients 65 years or older with NSTEMI in the PLATO study benefitted from ticagrelor only if managed without revascularisation (Lindholm et al., 2014), a finding that supports that an increased use of PCI may have implications for the results.

Our results indicate that the effects seen in the PLATO trial may not be fully applicable in current health care. In older patients, there seem little or no difference between clopidogrel and ticagrelor regarding beneficial effects and bleeding complications are more prominent.

For instance, clinically significant bleeding occurred in 14% of the study participants randomised to ticagrelor in the PLATO trial with a mean age of 62, whereas the corresponding figure was 24% in the study by Gimbel et al. (2020) with a mean age of 77 years. Interestingly, a recent Swedish non-RCT found that clopidogrel, compared with ticagrelor, was associated with an increased risk of all-cause death in those below 80 years, whereas as lower risk was seen in those 80 years or older (Szummer et al., 2020).

Overall completeness and applicability of evidence

Including patients at various ages with STEMI as well as NSTEMI and unstable angina, the present HTA applies broadly to ACS patients subjected to DAPT. However, the HTA does not include the subgroup of patients who also have indication for a direct-acting oral anticoagulant or warfarin, most often due to atrial fibrillation. These patients need platelets inhibition after ACS but clear recommendations are lacking regarding the decision of mono or dual antiplatelet therapy, as well as the duration of combination therapy.

Agreements and disagreements with other studies and reviews

In the literature search process, a total of 13 recent systematic reviews, relevant for our PICO and published in 2018-2020, were identified (Baldetti et al., 2020, Chen et al., 2020, Fan et al., 2019, Galimzhanov et al., 2019, Guan et al., 2018, Kheiri et al., 2018, Li et al., 2019, Misumida et al., 2018, Montalto et al., 2020, Navarese et al., 2020, Wang et al., 2018, Wu et al., 2018, Wu et al., 2020). The results of these, in relation to ours, are presented in Table 9.

There are several important differences between this HTA and previous systematic reviews on the topic. First, our review is more comprehensive, including 35 RCTs and 46 non-RCTs, compared with previous reviews including up to 16 RCTs and up to 13 non-RCTs. Thereby, the entire evidence base was reflected, however revealing the problems associated with zero-event trials. Second, we focused on the absolute risk difference, whereas all prior meta-analyses focus on risk ratios. Third, we analysed RCTs and non-RCTs separately, whereas some of the previous reviews combined RCTs and non-RCTs in the same meta-analyses (Fan et al., 2019, Guan et al., 2018, Li et al., 2019, Wang et al., 2018, Wu et al., 2020) or based their meta-analysis solely on non-RCTs (Galimzhanov et al., 2019). Fourth, we used GRADE to assess the certainty of evidence, whereas only one other systematic review, including two RCTs, stated to have used this system (Montalto et al., 2020). Fifth, angina, rehospitalisations and HRQL were not evaluated in any previous systematic review. Sixth, we analysed older patients as a separate group. This age group has been in focus in one prior review that only focused on bleedings (Montalto et al., 2020).

Table 9 Systematic reviews relevant for our PICO and published in 2018-2020. In this table, results favouring clopidogrel are coloured in green, results favouring ticagrelor in red, and non-significant/inconclusive results in grey. Outcomes without colour were not reported in the systematic review at issue.

Study	Patients	RCTs (n)	nRCTs (n)	All-cause mortality	CV mortality	MI	Clinically significant bleeding[3]	Major bleeding	Stent thrombosis	Angina	Rehospi-talisation	HRQL	Dyspnea
Current HTA	**ACS**[1]	**35**	**46**	⊕⊕◯◯	⊕⊕◯◯	⊕⊕⊕◯	⊕⊕⊕⊕	⊕⊕◯◯	⊕⊕⊕◯	⊕⊕◯◯	⊕◯◯◯	⊕⊕◯◯	⊕⊕⊕⊕
	ACS[2]					⊕⊕⊕◯	⊕⊕⊕⊕		⊕⊕⊕◯				⊕⊕⊕⊕
	ACS, older age	**2**	**2**	⊕⊕◯◯	⊕⊕◯◯	⊕⊕⊕◯	⊕⊕⊕◯	⊕⊕⊕◯	⊕◯◯◯				
Baldetti et al., 2020	ACS, network meta-analysis	4	3										
Chen et al., 2020	ACS, low dose ticagrelor	16	0										
Fan et al., 2019	ACS with PCI	6	5										
Galimzhanov et al., 2019	ACS, Asian patients	0	6										
Guan et al., 2018	ACS	11	5										
Kheiri et al., 2018	STEMI, fibrinolytic therapy	5	0										
Li et al., 2019	ACS, East Asian	4	3										
Misumida et al., 2018	ACS, East Asian	3	0										
Montalto et al., 2020	ACS, older age, network meta-analysis	2	0										
Navarese et al., 2020	ACS, network meta-analysis	6	0										
Wang et al., 2018	ACS	8	2										
Wu et al., 2018	ACS, East Asian	2	0										
Wu et al., 2020	ACS with PCI	5	13										

[1]Meta-anlysis including zero-event RCTs with continuity correction
[2]Meta-analysis excluding zero-event RCTs
[3]Including major bleedings as well as other bleedings requiring surgical or medical intervention
ACS = acute coronary syndrome, CV = cardiovascular, diff = difference, HRQL = health-related quality of life, MI = myocardial infarction, nRCT = non-randomised controlled trial, PCI = percutaneous coronary intervention, RCT = randomised controlled trial, STEMI = ST-elevation myocardial infarction

Implications for research

There are numerous studies investigating the PICO of this HTA. To contribute to an increased certainty of evidence, rigour in design and reporting of future studies will be essential. For instance, RCTs in relevant subgroups could be of value. Regarding non-RCTs, the methods used will have to consider that patient characteristics differ from start; those being prescribed clopidogrel are in general older and have a more complex medical condition compared with those being prescribed ticagrelor (Alexopoulos et al., 2016, Antoniou et al., 2018, De Filippo et al., 2019, Edfors et al., 2018, Gajanana et al., 2018, Grimaldi-Bensouda et al., 2018, Kim et al., 2019, Kim et al., 2017, Krishnamurthy et al., 2019, Lee et al., 2018, Ohman et al., 2017, Rasia et al., 2017, Sahlen et al., 2016, Sheikh Rezaei et al., 2017, Sim et al., 2019, Welsh et al., 2019, Vyas et al., 2017, Yudi et al., 2016, Zocca et al., 2017). We were pleased to notice that this basic challenge was better handled in the non-RCTs identified in the updated search (Ahn et al., 2020, Peyracchia et al., 2020, Sun et al., 2019, Szummer et al., 2020, Turgeon et al., 2020, Völz et al., 2020).

On the other hand, propensity score matching in non-RCT may have implications for the directness. In the 13 non-RCTs comparing propensity score matched groups, 8% to 78% of the clopidogrel-treated patients could be included (Ahn et al., 2020, Blin et al., 2019, Choe et al., 2019, Lee et al., 2018, Park et al., 2016, Peyracchia et al., 2020, Schmucker et al., 2019, Sim et al., 2018, Spoendlin et al., 2018, Sun et al., 2019, Turgeon et al., 2020, Wang et al., 2018, Yun et al., 2019).

In the process of this HTA, the difficulties in evaluating bleedings have become apparent. First, several different scales are used in the research within the field. Second, the term *major bleeding*, although seemingly covering what would be important for the patient and health care, does not sufficiently capture clinically significant bleedings. In fact, the term *minor bleeding* may in some scales also be insufficient in this respect. For instance, minor bleeding in the TIMI bleeding scale does not include all bleedings requiring surgical and medical interventions. In future CV research, a consensus on how to report bleedings, that is, which scale to be used and how to combine the categories in composite bleeding measures, would facilitate future compilations of the evidence base.

14. Future perspectives

Scientific knowledge gaps

Given that there were only low (all-cause mortality, HRQL) and very low (rehospitalisation) certainty evidence regarding outcomes reflecting the net effect of a clopidogrel- versus a ticagrelor-based DAPT, additional well-designed RCTs in current health care could be of value. In addition, there are several uncertainties regarding the effects in older patients, with low certainty evidence suggesting little or no difference in the all-cause mortality, CV mortality, and the risk of MI.

Ongoing research

The search in the Clinical trials database for ongoing studies identified 144 records, 38 of which corresponded to the PICO in this HTA. In all, 13 of these had already been published and were captured and/or handled in our literature search. Among the remaining 25 ongoing, but not published, studies, we found three RCTs being designed to investigate a composite of clinical events as primary outcome and therefore highly relevant for the question at issue (Table 10).

Table 10 Ongoing RCTs according to ClinicalTrials.gov corresponding to the PICO of this report, and designed to investigate a composite of clinical events as primary outcome

Trial number Country	Study description	Primary outcome	Estimated enrollment	Expected completion date
NCT04057300 Canada	RCT comparing ticagrelor and clopidogrel in patients with ACS, conducted in the North American region (in the PLATO trial, results in this region differed from those in other regions)	Composite of CV mortality, MI, or stroke	1,500 patients	2021
NCT03357874 France	RCT comparing ticagrelor and clopidogrel in patients with severe or terminal chronic kidney disease and ACS treated with PCI	Composite of major adverse cardiovascular events death, MI, urgent revascularisation, and stroke at 1 year	514 patients	2023
NCT03150667 United States	RCT comparing ticagrelor and clopidogrel in patients with chronic kidney disease (eGFR<60 mL/min per 1.73 m^2) and ACS	Composite of all-cause mortality, MI, or stroke within 1 year	220 patients	2020

Another 17 RCTs were identified that could contribute information regarding our PICO. However, as they are primarily designed to address other aspects than clinical events, for instance pharmacodynamic properties, and have outcomes at issue in this HTA as secondary endpoints, they are unlikely to affect the conclusions of this HTA (NCT01738100, NCT02699008, NCT03775746, NCT01812330, NCT01930591, NCT02123004, NCT02201667, NCT02224534, NCT02244710, NCT02415803, NCT02578537, NCT02639143, NCT02798874, NCT02944123, NCT03415386, NCT04060914, NCT04174261).

In addition, five non-RCTs, relevant for our PICO, were identified in our search for ongoing studies. One cohort study from China aims to include 9,000 ACS patients treated with PCI and is estimated to be completed in 2021 (NCT03239067); published interim results are included in the present HTA (Sun et al., 2019). Two non-RCTs have both been completed in 2016 but are not yet published – one case-control study of 4,992 ACS patients in France analysing recurrent MI (NCT01952392), and one before/after study of 5,225 patients with ACS in the United Kingdom with focus on major bleedings before and after the implementation of new guidelines (NCT02484924). One cohort study from Spain aims to compare different types of, and duration of, dual antiplatelet therapy regarding the primary endpoint all-cause mortality up to three years after ACS in 8,000 patients (NCT03664388). This study was expected to be completed in 2020, but the recruitment status is currently unknown. Another cohort study from Spain, with an estimated completion date in 2021, aims to include 2,000 ACS patients with the primary aim to study the type of antiplatelet treatment used; ischemic and bleeding events are secondary outcomes (NCT02500290).

15. Participants in the project

The question was nominated by

Charlotta Ljungman, MD, PhD, Head of Department of Cardiology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating healthcare professionals

Niklas Bergh, MD, PhD, Associate Professor, Region Västra Götaland, Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden
Anna Myredal, MD, PhD, Region Västra Götaland, Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden
Per Nivedahl, MD, Region Västra Götaland, Department of Cardiology and Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden
Sultan Zarin, MD, Region Västra Götaland, Department of Cardiology, Kungälv Hospital, Kungälv, Sweden

Participants from the HTA-centrum, Region Västra Götaland

Ann Liljegren, HTA librarian
Max Petzold, statistician, professor
Henrik Sjövall, MD, professor
Ida Stadig, HTA librarian
Mikael Svensson, health economist, professor
Constanze Wartenberg, psychologist, PhD
Susanna M Wallerstedt, MD, professor
Pernilla Rönnholm, project coordinator

External reviewers

Anna-Lena Eriksson, MD, PhD, Region Västra Götaland, Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden, Department of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Gothenburg
Lars Grip, MD, professor emeritus, Region Västra Götaland, Sahlgrenska University Hospital

Declaration of interests

A Myredal, N Bergh, P Nivedahl, S Zarin, M Petzold, H Sjövall and SM Wallerstedt declare no conflicts of interest.
C Wartenberg worked for AstraZeneca between 2004 and 2016.
AL Eriksson declares that her partner works as a preclinical researcher in AstraZeneca. She also performs and publishes pedagogic research with SM Wallerstedt.
L Grip declares no conflicts of interest.

Project time

The HTA was accomplished during the period of August 29th 2019 – May 19th 2021.
Literature searches were made on September 13th 2019, with an update on September 2nd 2020.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
In ACS patients subjected to DAPT, including those of older age, is clopidogrel combined with ASA similar to ticagrelor combined with ASA, regarding the outcomes mortality, MI, bleeding, stent thrombosis, angina, rehospitalisation, health-related quality of life (HRQL), and dyspnea?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P	P1: Adult (>18 years) patients subjected to DAPT in ACS (MI with or without ST elevation, unstable angina) P2: Older (>65 years) patients subjected to DAPT in ACS (MI with or without ST elevation, unstable angina)
I	Clopidogrel + ASA
C	Ticagrelor + ASA
O	Critical for decision making • Mortality (all-cause, cardiovascular) • MI • Bleeding (clinically significant, major) • Stent thrombosis • Angina Important for decision making • Rehospitalisation • Health related quality of life (HRQL) • Dyspnea

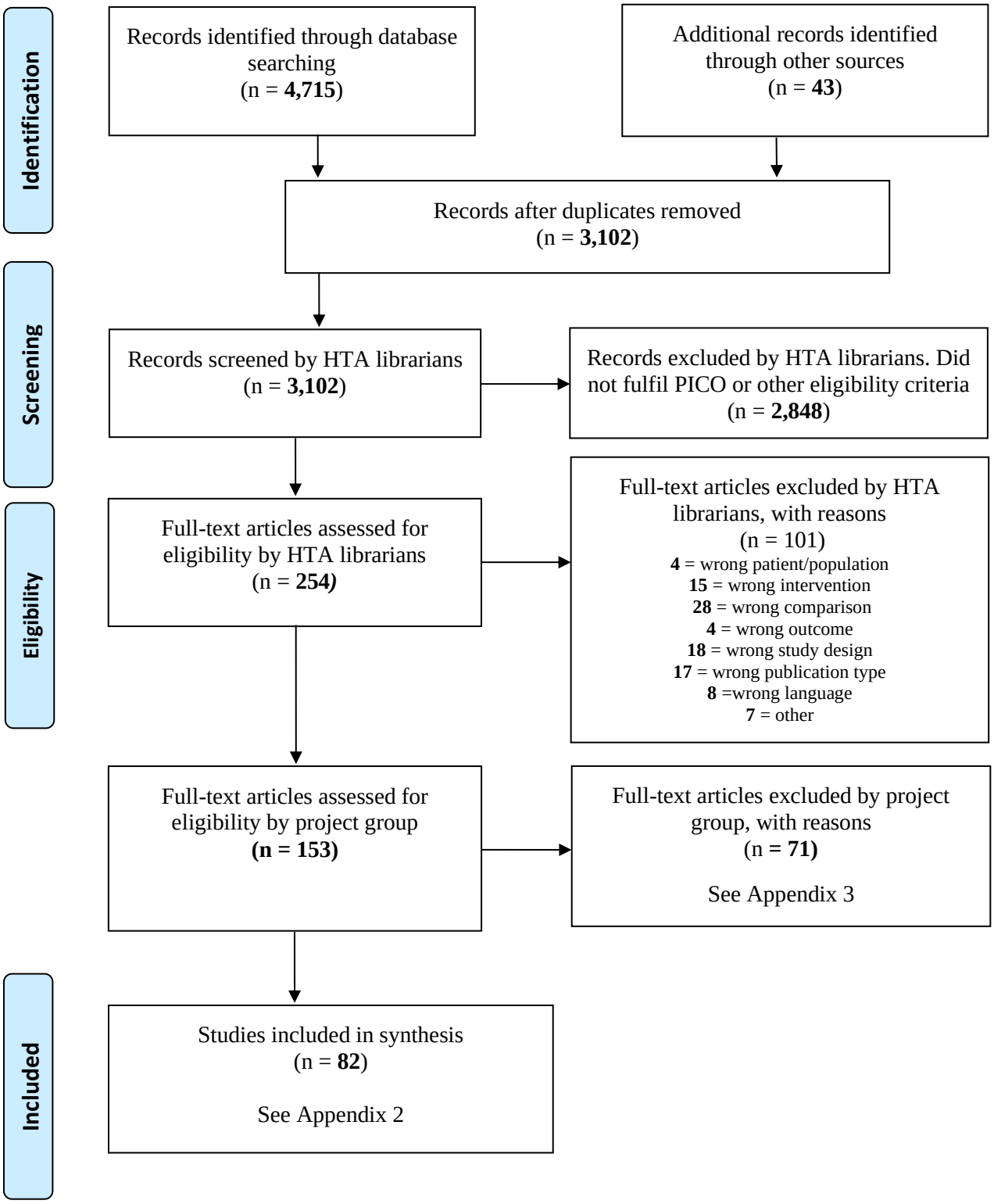
Eligibility criteria

Study design:
Randomised controlled trial
Non-randomised controlled trials including >500 patients

Language:
English, Swedish, Danish or Norwegian

Publication date: 2005-

Selection process – flow diagram



Modified from Moher et al., 2009

Database: Embase 1974 to 2019 September 12 (OvidSP)
Date: 13 Sep 2019
No. of results: 2463
Search updated: 200902, 348 results

#	Searches	Results
1	exp acute heart infarction/ or exp non ST segment elevation myocardial infarction/ or exp ST segment elevation myocardial infarction/ or exp non st segment elevation acute coronary syndrome/ or exp unstable angina pectoris/	124580
2	STEMI.ab,kw,ti.	26449
3	(ST adj4 (elevat* or segment)).ab,kw,ti.	57286
4	NSTEMI.ab,kw,ti.	6941
5	(non STEMI or non-STEMI).ab,kw,ti.	1270
6	((Non-st or Non st) adj4 (elevat* or segment)).ab,kw,ti.	10647
7	(Acute adj3 (Myocardial Infarct* or Coronary Syndrome* or cardiac infarct* or Heart infarct* or MI or Heart Attack*)).ab,ti,kw.	141459
8	(Unstable angina* or Preinfarction Angina* or Pre-infarction Angina* or Pre infarction Angina* or Angina at rest or Variant angina* or Prinzmetals angina*).ab,kw,ti.	21855
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	216436
10	exp ticagrelor/	8022
11	(Ticagrelor or Tikagrelor or Brilinta or Brilique or Possia or AZD 6140 or AZD6140 or AZD-6140).mp.	8403
12	10 or 11	8403
13	exp clopidogrel/	57776
14	(Clopidogrel or SC 25989C or SC25989C or SC-25989C or SC 25990C or SC25990C or SC-25990C or SR 25989 or SR25989 or SR-25989 or Iscover or PCR 4099 or PCR4099 or PCR-4099 or Plavix or Clopilet or grepid or zopya or Zylagren or zyllt).mp.	59637
15	13 or 14	59637
16	9 and 12 and 15	3858
17	(animal not (animal and human)).sh.	1047674
18	16 not 17	3858
19	(child not (child and adult)).sh.	1110949
20	18 not 19	3857
21	limit 20 to (danish or english or norwegian or swedish)	3681
22	limit 21 to (embase or medline)	2845
23	limit 22 to (article or article in press or conference paper or "review")	2465
24	limit 23 to yr="2005 -Current"	2463

Database: Ovid MEDLINE(R) ALL 1946 to September 12, 2019
Date: 13 Sep 2019
No. of results: 909
Search updated: 200902, 148 results

#	Searches	Results
1	exp st elevation myocardial infarction/ or exp non-st elevated myocardial infarction/ or exp angina, unstable/	13967
2	STEMI.ab,kf,ti.	10052
3	(ST adj4 (elevat* or segment)).ab,kf,ti.	34169
4	NSTEMI.ab,kf,ti.	2194
5	(non STEMI or non-STEMI).ab,kf,ti.	489
6	((Non-st or Non st) adj4 (elevat* or segment)).ab,kf,ti.	6089
7	(Acute adj3 (Myocardial Infarct* or Coronary Syndrome* or cardiac infarct* or heart infarct* or MI or Heart Attack*)).ab,kf,ti.	92344
8	(Unstable angina* or Preinfarction Angina* or Pre-infarction Angina* or Pre infarction Angina* or Angina at rest or Variant angina* or Prinzmetals angina*).ab,kf,ti.	14745
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	123489
10	exp Ticagrelor/	1268
11	(Ticagrelor or Tikagrelor or Brilinta or Brilique or Possia or AZD 6140 or AZD6140 or AZD-6140).ab,kf,ti.	2310
12	10 or 11	2452
13	exp Clopidogrel/	8508
14	(Clopidogrel or SC 25989C or SC25989C or SC-25989C or SC 25990C or SC25990C or SC-25990C or SR 25989 or SR25989 or SR-25989 or Iscover or PCR 4099 or PCR4099 or PCR-4099 or Plavix or Clopilet or grepid or zopya or Zylagren or zyllt).ab,kf,ti.	12148
15	13 or 14	13829
16	9 and 12 and 15	1027
17	(animals not (animals and humans)).sh.	4581939
18	16 not 17	1025
19	(child not (child and adult)).sh.	1027180
20	18 not 19	1024
21	limit 20 to (danish or english or norwegian or swedish)	954
22	(comment or editorial or letter).pt.	1762427
23	21 not 22	909
24	limit 23 to yr="2005 -Current"	909

Database: The Cochrane Library
Date: 13 Sep 2019
No. of results: 448
Trials 448
Search updated: 200902, 73 results

ID	Search	Hits
#1	MeSH descriptor: [ST Elevation Myocardial Infarction] explode all trees	322
#2	MeSH descriptor: [Non-ST Elevated Myocardial Infarction] explode all trees	57
#3	MeSH descriptor: [Angina, Unstable] explode all trees	1057
#4	(STEMI):ti,ab,kw	2999
#5	((ST NEAR/4 (elevat* OR segment))):ti,ab,kw	8350
#6	(NSTEMI):ti,ab,kw	494
#7	("non STEMI" OR non-STEMI):ti,ab,kw	94
#8	(((Non-st OR "Non st") NEAR/4 (elevat* OR segment))):ti,ab,kw	1827
#9	((Acute NEAR/3 ("Myocardial Infarct*" OR "Coronary Syndrome*" OR "cardiac infarct*" OR "heart infarct*" OR MI OR "Heart Attack*"))):ti,ab,kw	6530
#10	("Unstable angina*" OR "Preinfarction Angina*" OR "Pre-infarction Angina*" OR "Pre infarction Angina*" OR "Angina at rest" OR "Variant angina*" OR "Prinzmetals angina*"):ti,ab,kw	3674
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	15925
#12	MeSH descriptor: [Ticagrelor] explode all trees	318
#13	(Ticagrelor OR Tikagrelor OR Brilinta OR Brilique OR Possia OR "AZD 6140" OR AZD6140 OR AZD-6140):ti,ab,kw	1424
#14	#12 OR #13	1424
#15	MeSH descriptor: [Clopidogrel] explode all trees	1358
#16	(Clopidogrel OR "SC 25989C" OR SC25989C OR SC-25989C OR "SC 25990C" OR SC25990C OR SC-25990C OR "SR 25989" OR SR25989 OR SR-25989 OR Iscover OR "PCR 4099" OR PCR4099 OR PCR-4099 OR Plavix OR Clopilet OR grepid OR zopya OR Zylagren OR zyllt):ti,ab,kw	5223
#17	#15 OR #16	5223
#18	#11 AND #14 AND #17	559
#19	(clinicaltrials or trialsearch):so	264602
#20	#18 NOT #19 with Cochrane Library publication date Between Jan 2005 and Sep 2019	448

Database: PubMed
Date: 13 Sep 2019
No. of results: 203
Search updated: 200902, 123 results

Search	Query	Items found
#13	**Search #11 AND #12**	**203**
#12	Search (pubmednotmedline[sb] OR inprocess[sb] OR publisher[sb])	3976672
#11	Search #8 AND #9 AND #10	996
#10	Search Clopidogrel[tiab] OR SC 25989C[tiab] OR SC25989C[tiab] OR SC-25989C[tiab] OR SC 25990C[tiab] OR SC25990C[tiab] OR SC-25990C[tiab] OR SR 25989[tiab] OR SR25989[tiab] OR SR-25989[tiab] OR Iscover[tiab] OR PCR 4099[tiab] OR PCR4099[tiab] OR PCR-4099[tiab] OR Plavix[tiab] OR Clopilet[tiab] OR grepid[tiab] OR zopya[tiab] OR Zylagren[tiab] OR zyllt[tiab]	12133
#9	Search Ticagrelor[tiab] OR Tikagrelor[tiab] OR Brilinta[tiab] OR Brilique[tiab] OR Possia[tiab] OR AZD 6140[tiab] OR AZD6140[tiab] OR AZD-6140[tiab]	2305
#8	Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	131038
#7	Search Unstable angina*[tiab] OR Preinfarction Angina*[tiab] OR Pre-infarction Angina*[tiab] OR Pre infarction Angina*[tiab] OR Angina at rest[tiab] OR Variant angina*[tiab] OR Prinzmetals angina*[tiab]	14396

#6	Search (Acute[tiab] AND (Myocardial Infarct*[tiab] OR Coronary Syndrome*[tiab] OR cardiac infarct*[tiab] OR heart infarct*[tiab] OR MI[tiab] OR Heart Attack*[tiab]))	103860
#5	Search ((Non-st[tiab] OR Non st[tiab]) AND (elevat*[tiab] OR segment[tiab]))	6072
#4	Search non STEMI[tiab] OR non-STEMI[tiab]	489
#3	Search NSTEMI[tiab]	2190
#2	Search (ST[tiab] AND (elevat*[tiab] OR segment[tiab]))	36221
#1	Search STEMI[tiab]	10051

The web-sites of **SBU** and **Folkehelseinstituttet** were visited
13 Sep 2019
Nothing relevant to the question at issue was found

Reference lists
A comprehensive review of reference lists brought 42 new records

---

Reference lists

Included studies:

Ahn JH, Ahn Y, Jeong MH, Kim JH, Hong YJ, Sim DS, et al. Ticagrelor versus clopidogrel in acute myocardial infarction patients with multivessel disease; From Korea Acute Myocardial Infarction Registry-National Institute of Health. J Cardiol. 2020;75(5):478-84. doi: 10.1016/j.jjcc.2019.11.003.

Alexopoulos D, Perperis A, Koniari I, Karvounis H, Patsilinakos S, Ziakas A, et al. Ticagrelor versus high dose clopidogrel in ST-segment elevation myocardial infarction patients with high platelet reactivity post fibrinolysis. J Thromb Thrombolysis. 2015;40(3):261-7. doi: 10.1007/s11239-015-1183-9

Alexopoulos D, Xanthopoulou I, Deftereos S, Hamilos M, Sitafidis G, Kanakakis I, et al. Contemporary antiplatelet treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: 1-year outcomes from the GReek AntiPlatElet (GRAPE) Registry. J Thromb Haemost. 2016;14(6):1146-54. doi: 10.1111/jth.13316.

Alexopoulos D, Xanthopoulou I, Perperis A, Goudevenos J, Hamilos M, Sitafidis G, et al. Dyspnea in patients treated with P2Y12 receptor antagonists: insights from the GReek AntiPlatElet (GRAPE) registry. Platelets. 2017;28(7):691-7. doi: 10.1080/09537104.2016.1265919.

Angiolillo D, Franchi F, Waksman R, Sweeny J, Raveendran G, Teng R, et al. Effects of ticagrelor versus clopidogrel in troponin-negative patients with low-risk ACS undergoing ad hoc PCI. J Am Coll Cardiol. 2016;67(6):603-13. doi: 10.1016/j.jacc.2015.11.044.

Antoniou S, Colicchia M, Guttmann OP, Rathod KS, Wright P, Fhadil S, et al. Risk scoring to guide antiplatelet therapy post-percutaneous coronary intervention for acute coronary syndrome results in improved clinical outcomes. Eur Heart J Qual Care Clin Outcomes. 2018;4(4):283-9. doi: 10.1093/ehjqcco/qcx041.

Berwanger O, Lopes RD, Moia DDF, Fonseca FA, Jiang L, Goodman SG, et al. Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis: TREAT Trial. J Am Coll Cardiol. 2019;73(22):2819-28. doi: 10.1016/j.jacc.2019.03.011.

Blin P, Dureau-Pournin C, Benichou J, Bonello L, Dallongeville J, Danchin N, et al. Secondary prevention of acute coronary events with antiplatelet agents (SPACE-AA): One-year real-world effectiveness and safety cohort study in the French nationwide claims database. Atherosclerosis. 2019;281:98-106. doi: 10.1016/j.atherosclerosis.2018.11.037.

Brener SJ, Alapati V, Benson MM, Chan D, Cunn G, Khan S, et al. Ticagrelor vs Clopidogrel in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention: Insights From a Single Institution Registry. J Invasive Cardiol. 2019;31(8):235-8.

Cannon C, Husted S, Harrington R, Scirica B, 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. J Am Coll Cardiol. 2007;50(19):1844-51. doi: 10.1016/j.jacc.2007.07.053.

Cao B, Qu F, Liu X, Gao C, Fu Q, Jiang C, et al. Short-term efficacy of ticagrelor in acute ST-segment elevation myocardial infarction patients undergoing an emergency percutaneous coronary intervention. Aging. 2019;11(20):8925-36. doi: 10.18632/aging.102353.

Chang CJ, Tung YC, Liu JR, Chang SH, Kuo CT, See LC. Efficacy and Safety of Ticagrelor versus Clopidogrel in East Asian Patients with Acute Myocardial Infarction: A Nationwide Cohort Study. Clin Pharmacol Ther. 2020. doi: 10.1002/cpt.2011.

Choe JC, Cha KS, Ahn J, Park JS, Lee HW, Oh JH, et al. Comparison of prescription rates and clinical outcomes in acute coronary syndrome patients who underwent percutaneous coronary intervention using different P2Y12 inhibitors in a large observational study. Int J Cardiol. 2019;274:21-6. doi: 10.1016/j.ijcard.2018.09.011.

De Filippo O, D'Ascenzo F, Raposeiras-Roubin S, Abu-Assi E, Peyracchia M, Bocchino PP, et al. P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects. Eur Heart J Cardiovasc Pharmacother. 2019;12:pvz048. doi: 10.1093/ehjcvp/pvz048.

Dehghani P, Lavoie A, Lavi S, Crawford J, Harenberg S, Zimmermann R, et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. Am Heart J. 2017;192:105-12. doi: 10.1016/j.ahj.2017.07.013.

Edfors R, Sahlen A, Szummer K, Renlund H, Evans M, Carrero JJ, et al. Outcomes in patients treated with ticagrelor versus clopidogrel after acute myocardial infarction stratified by renal function. Heart. 2018;104(19):1575-82. doi: 10.1136/heartjnl-2017-312436.

Gajanana D, Weintraub WS, Kolm P, Rogers T, Iantorno M, Buchanan KD, et al. The impact of in-hospital P2Y12 inhibitor switch in patients with acute coronary syndrome. Cardiovasc Revasc Med. 2018;19(8):912-6. doi: 10.1016/j.carrev.2018.09.007.

Gasecka A, Nieuwland R, Budnik M, Dignat-George F, Eyileten C, Harrison P, et al. Ticagrelor attenuates the increase of extracellular vesicle concentrations in plasma after acute myocardial infarction compared to clopidogrel. J Thromb Haemost. 2020;18(3):609-23. doi: 10.1111/jth.14689.

Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet. 2020;395(10233):1374-81. doi: https://dx.doi.org/10.1016/S0140-6736(20)30325-1.

Giordana F, Montefusco A, D'Ascenzo F, Moretti C, Scarano S, Abu-Assi E, et al. Safety and effectiveness of the new P2Y12r inhibitor agents vs clopidogrel in ACS patients according to the geographic area: East Asia vs Europe. Int J Cardiol. 2016;220:488-95. doi: 10.1016/j.ijcard.2016.06.063.

Gosling R, Yazdani M, Parviz Y, Hall IR, Grech ED, Gunn JP, et al. Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive 'real-world' patients. Platelets. 2017;28(8):767-73. doi: 10.1080/09537104.2017.1280601.

Goto S, Huang C, Park S, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome -- randomized, double-blind, phase III PHILO study. Circ J. 2015;79(11):2452-60. doi: 10.1253/circj.CJ-15-0112

Grimaldi-Bensouda L, Danchin N, Dallongeville J, Falissard B, Furber A, Cottin Y, et al. Effectiveness of new antiplatelets in the prevention of recurrent myocardial infarction. Heart. 2018;104(19):1583-92. doi: 10.1136/heartjnl-2017-312534.

Gu X, Fu X, Wang Y, Zhang W, Fan W, Jiang Y, et al. Comparison of ticagrelor and high-dose clopidogrel on the platelet functions in patients with inadequate response to clopidogrel. Am J Cardiovasc Dis. 2017;7(1):1-8.

Hansson EC, Jideus L, Aberg B, Bjursten H, Dreifaldt M, Holmgren A, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: A nationwide study. Eur Heart J. 2016;37(2):189-97. doi: 10.1093/eurheartj/ehv381.

Jing R, Lin W. Comparison of ticagrelor with clopidogrel in Chinse ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. Int J Clin Exp Med. 2016;9(12):23525-9.

Kang J, Han JK, Ahn Y, Chae SC, Kim YJ, Chae IH, et al. Third-Generation P2Y 12 Inhibitors in East Asian Acute Myocardial Infarction Patients: A Nationwide Prospective Multicentre Study. Thromb Haemost. 2017;118(3):591-600. doi: 10.1055/s-0038-1626697.

Kim C, Kim BK, Hong SJ, Ahn CM, Kim JS, Ko YG, et al. Randomized comparison of strut coverage between ticagrelor and clopidogrel in acute myocardial infarction at 3-month optical coherence tomography. Yonsei Med J. 2018;59(5):624-32. doi: 10.3349/ymj.2018.59.5.624.

Kim C, Shin DH, Hong SJ, Ahn CM, Kim JS, Kim BK, et al. One-year clinical outcomes of ticagrelor compared with clopidogrel after percutaneous coronary intervention in patients with acute myocardial infarction: From Korean Health Insurance Review and Assessment Data. J Cardiol. 2019;73(3):191-7. doi: 10.1016/j.jjcc.2018.08.005.

Kim K, Lee TA, Ardati AK, DiDomenico RJ, Touchette DR, Walton SM. Comparative Effectiveness of Oral Antiplatelet Agents in Patients with Acute Coronary Syndrome. Pharmacotherapy. 2017;37(8):877-87. doi: 10.1002/phar.1961.

Krackhardt F, Waliszewski M, Kočka V, Toušek P, Janek B, Hudec M, et al. Real-World Dual Antiplatelet Therapy Following Polymer-Free Sirolimus-Eluting Stent Implantations to Treat Coronary Artery Disease. Cardiovasc Drugs Ther. 2020;34(3):335-44. doi: 10.1007/s10557-020-06963-5.

Krishnamurthy A, Keeble C, Anderson M, Somers K, Burton-Wood N, Harl, et al. Real-world comparison of clopidogrel, prasugrel and ticagrelor in patients undergoing primary percutaneous coronary intervention. Open Heart. 2019;6(1):e000951. doi: 10.1136/openhrt-2018-000951.

Lee CH, Cheng CL, Kao Yang YH, Chao TH, Chen JY, Li YH. Cardiovascular and bleeding risks in acute myocardial infarction newly treated with ticagrelor vs. Clopidogrel in Taiwan. Circ J 2018;82(3):747-56. doi: 10.1253/circj.CJ-17-0632.

Levin L, Wallentin L, Bernfort L, Andersson D, Storey R, Bergström G, et al. Health-related quality of life of ticagrelor versus clopidogrel in patients with acute coronary syndromes-results from the PLATO trial. Value Health. 2013;16(4):574-80. doi: 10.1016/j.jval.2013.01.013.

Li P, Yang Y, Chen T, Liu Y, Cao A, Liu J, et al. Ticagrelor overcomes high platelet reactivity in patients with acute myocardial infarction or coronary artery in-stent restenosis: a randomized controlled trial. Sci Rep. 2015;5:13789. doi: 10.1038/srep13789.

Li X, Su G, Wang G, Hu H, Fan C. Switching from ticagrelor to clopidogrel in patients with ST-segment elevation myocardial infarction undergoing successful percutaneous coronary intervention in real-world China: occurrences, reasons, and long-term clinical outcomes. Clin Cardiol. 2018;41(11):1446-54. doi: 10.1002/clc.23074.

Liu GZ, Zhang S, Sun DH, Shi J, Bo WL, Wang WN, et al. Half-dose ticagrelor versus high-dose clopidogrel in reducing platelet reactivity in acute coronary syndrome patients with high on-clopidogrel platelet reactivity (divide study). Eur J Clin Pharmacol. 2019a;75(8):1059-68. doi: 10.1007/s00228-019-02687-0.

Liu Y, Ding LY, Li XZ. Therapy with ticagrelor for ST-elevated acute coronary syndrome accompanied by diabetes mellitus. Eur Rev Med Pharmacol Sci. 2019b;23(3):312-8. doi: 10.26355/eurrev_201908_18662.

Liu Y, Liu H, Hao Y, Hao Z, Geng G, Han W, et al. Short-term efficacy and safety of three different antiplatelet regimens in diabetic patients treated with primary percutaneous coronary intervention: a randomised study. Kardiol Pol. 2017;75(9):850-8. doi: 10.5603/KP.a2017.0116.

Lu Y, Li Y, Yao R, Li Y, Li L, Zhao L, et al. Clinical effect of ticagrelor administered in acute coronary syndrome patients following percutaneous coronary intervention. Exp Ther Med. 2016;11(6):2177-84. doi: 10.3892/etm.2016.3224.

Mohareb MW, AbdElghany M, Zaki HF, El-Abhar HS. Diabetes and CYP2C19 Polymorphism Synergistically Impair the Antiplatelet Activity of Clopidogrel Compared to Ticagrelor in PCI-Treated ACS Patients. J Cardiovasc Pharmacol. 2020. doi: 10.1097/fjc.0000000000000881.

Ohman E, Roe M, Steg P, James S, Povsic T, White J, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet. 2017;389(10081):1799-808. doi: 10.1016/S0140-6736(17)30751-1.

Olier I, Sirker A, Hildick-Smith D, Kinnaird T, Ludman P, De BM, et al. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. Heart. 2018;104(20):1683-90. doi: 10.1136/heartjnl-2017-312366.

Orenes-Pinero E, Esteve-Pastor MA, Ruiz-Nodar JM, Quintana-Giner M, Veliz-Martinez A, Tello-Montoliu A, et al. Under-prescription of novel antiplatelet drugs in patients with acute coronary syndrome and previous cardiovascular disease. Minerva Medica. 2019;110(5):410-8. doi: 10.23736/S0026-4806.19.05859-2.

Park DW, Kwon O, Jang JS, Yun SC, Park H, Kang DY, et al. Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management: a Randomized Clinical Trial. Circulation. 2019a;140(23):1865-77. doi: 10.1161/circulationaha.119.041766.

Park K, Cho YR, Park JS, Park TH, Kim MH, Kim YD. Comparison of the Effects of Ticagrelor and Clopidogrel on Microvascular Dysfunction in Patients With Acute Coronary Syndrome Using Invasive Physiologic Indices. Circ Cardiovasc Interv. 2019b;12(10):e008105. doi: 10.1161/circinterventions.119.008105.

Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; From Korea Acute Myocardial Infarction Registry - National Institute of Health. Int J Cardiol. 2016;215:193-200. doi: 10.1016/j.ijcard.2016.04.044.

Peyracchia M, Saglietto A, Biolè C, Raposeiras-Roubin S, Abu-Assi E, Kinnaird T, et al. Efficacy and Safety of Clopidogrel, Prasugrel and Ticagrelor in ACS Patients Treated with PCI: A Propensity Score Analysis of the RENAMI and BleeMACS Registries. Am J Cardiovasc Drugs. 2020;20(3):259-69. doi: 10.1007/s40256-019-00373-1.

Rasia M, Solinas E, Marino M, Guastaroba P, Menozzi A, Cattabiani M, et al. Comparison of 4 different strategies of DAPT after PCI in ACS real world population from a Northern Italy registry. J Thromb Thrombolysis. 2017;44(4):466-74. doi: 10.1007/s11239-017-1567-0.

Sahlen A, Varenhorst C, Lagerqvist B, Renlund H, Omerovic E, Erlinge D, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: Experiences from SWEDEHEART registry. Eur Heart J. 2016;37(44):3335-42. doi: 10.1093/eurheartj/ehw284.

Schmucker J, Fach A, Mata Marin LA, Retzlaff T, Osteresch R, Kollhorst B, et al. Efficacy and Safety of Ticagrelor in Comparison to Clopidogrel in Elderly Patients With ST-Segment-Elevation Myocardial Infarctions. J Am Heart Assoc. 2019;8(18):e012530. doi: 10.1161/jaha.119.012530.

Sheikh Rezaei S, Geroldinger A, Heinze G, Reichardt B, Wolzt M. Clopidogrel, prasugrel, or ticagrelor use and clinical outcome in patients with acute coronary syndrome: A nationwide long-term registry analysis from 2009 to 2014. Int J Cardiol. 2017;235:61-6. doi: 10.1016/j.ijcard.2017.02.096.

Sim DS, Jeong MH, Kim HS, Gwon HC, Seung KB, Rha SW, et al. Utility of GRACE and ACUITY-HORIZONS risk scores to guide dual antiplatelet therapy in Korean patients with acute myocardial infarction undergoing drug-eluting stenting. J Cardiol. 2018;72(5):411-9. doi: 10.1016/j.jjcc.2018.04.006.

Sim DS, Jeong MH, Kim HS, Gwon HC, Seung KB, Rha SW, et al. Association of potent P2Y12 blockers with ischemic and bleeding outcomes in non-ST-segment elevation myocardial infarction. J Cardiol. 2019;73(2):142-50. doi: 10.1016/j.jjcc.2018.09.002.

Spoendlin J, Gagne JJ, Lewey JJ, Patorno E, Schneeweiss S, Desai RJ. Comparative effectiveness and safety of antiplatelet drugs in patients with diabetes mellitus and acute coronary syndrome. Pharmacoepidemiol Drug Saf. 2018;27(12):1361-70. doi: 10.1002/pds.4668.

Sun Y, Li C, Zhang L, Yu T, Ye H, Yu B, et al. Clinical outcomes after ticagrelor and clopidogrel in Chinese post-stented patients. Atherosclerosis. 2019;290:52-8. doi: 10.1016/j.atherosclerosis.2019.09.011.

Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, et al. Comparison Between Ticagrelor and Clopidogrel in Elderly Patients with an Acute Coronary Syndrome: Insights from the SWEDEHEART Registry. Circulation. 2020. doi: 10.1161/circulationaha.120.050645.

Tang X, Li R, Jing Q, Wang Q, Liu P, Zhang P, et al. Assessment of Ticagrelor Versus Clopidogrel Treatment in Patients With ST-elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. J Cardiovasc Pharmacol. 2016;68(2):115-20. doi: 10.1097/FJC.0000000000000390.

Turgeon RD, Koshman SL, Youngson E, Har B, Wilton SB, James MT, et al. Association of Ticagrelor vs Clopidogrel With Major Adverse Coronary Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. JAMA Intern Med. 2020;180(3):420-8. doi: 10.1001/jamainternmed.2019.6447.

Wallentin L, Becker R, Budaj A, Cannon C, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57. doi: 10.1056/NEJMoa0904327.

Wang H, Wang X. Efficacy and safety outcomes of ticagrelor compared with clopidogrel in elderly Chinese patients with acute coronary syndrome. Ther Clin Risk Manag. 2016a;12:1101-5. doi: 10.2147/TCRM.S108965.

Wang HY, Li Y, Xu XM, Li J, Han YL. Impact of baseline bleeding risk on efficacy and safety of ticagrelor versus clopidogrel in Chinese patients with acute coronary syndrome undergoing percutaneous coronary intervention. Chin Medl J. 2018;131(17):2017-24. doi: 10.4103/0366-6999.239306.

Wang S, Yang X, Li Z, Zhang B, Cheng Y. Safety and efficacy of ticagrelor with emergency percutaneous coronary intervention in senile patients with ST-segment elevation myocardial infarction and dementia. Int J Clin Exp Med. 2016b;9(6):11831-7.

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. Coron Artery Dis. 2019;30(5):317-22. doi: 10.1097/MCA.0000000000000707.

Welsh RC, Sidhu RS, Cairns JA, Lavi S, Kedev S, Moreno R, et al. Outcomes Among Clopidogrel, Prasugrel, and Ticagrelor in ST-Elevation Myocardial Infarction Patients Who Underwent Primary Percutaneous Coronary Intervention From the TOTAL Trial. Can J Cardiol. 2019;35:1377-85. doi: 10.1016/j.cjca.2019.04.026.

Wu HB, Tian HP, Wang XC, Bai SR, Li XN, Zhang LN, et al. Clinical efficacy of ticagrelor in patients undergoing emergency intervention for acute myocardial infarction and its impact on platelet aggregation rate. Am J Transl Res. 2018;10(7):2175-83.

Vyas A, Bash LD, Patel MD, Simpson RJ. Changes in treatment patterns and incremental health care utilization due to P2Y12-associated complications in patients with acute coronary syndrome. J Manag Care Spec Pharm. 2017;23(9):947-56. doi: 10.18553/jmcp.2017.23.9.947.

Völz S, Petursson P, Odenstedt J, Ioanes D, Haraldsson I, Angerås O, et al. Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry. J Am Heart Assoc. 2020;9(14):e015990. doi: 10.1161/jaha.119.015990.

Xin YG, Li JL, Cao X, Liu XJ. Efficacy and Safety of Different Antiplatelet Strategies in Survivors of Myocardial Infarction With Acute Coronary Syndrome. Clin Ther. 2019;41:2090-2101. doi: 10.1016/j.clinthera.2019.08.007.

Xiong R, Liu W, Chen L, Kang T, Ning S, Li J. A randomized controlled trial to assess the efficacy and safety of doubling dose clopidogrel versus ticagrelor for the treatment of acute coronary syndrome in patients with CYP2C19*2 homozygotes. Int J Clin Exp Med. 2015;8(8):13310-6.

Xue H, Shi J, Liu B, Wang D, Dong Z, Guo H, et al. Comparison of half- and standard-dose ticagrelor in Chinese patients with NSTE-ACS. Platelets. 2016;27(5):440-5. doi: 10.3109/09537104.2015.1135890.

Yan Y, Wang X, Fan JY, Nie SP, Raposeiras-Roubin S, Abu-Assi E, et al. Impact of concomitant use of proton pump inhibitors and clopidogrel or ticagrelor on clinical outcomes in patients with acute coronary syndrome. J Geriatr Cardiol. 2016;13(3):209-17. doi: 10.11909/j.issn.1671-5411.2016.03.007.

Yang B, Zheng C, Yu H, Zhang R, Li S, Len M, et al. Comparison of Efficacy between Clopidogrel and Ticagrelor in Patients with Acute Coronary Syndrome after Interventional Treatment and Their Effects on IL-6. Iran J Public Health. 2020;49(2):240-8.

Yang B, Zheng C, Yu H, Zhang R, Li S, Tan L, et al. Comparison of Ticagrelor and Clopidogrel for Patients Undergoing Emergency Percutaneous Coronary Intervention. Iran J Public Health. 2018;47(7):952-7.

Yao Z, Fu C, Li G. Analysis of antiplatelet activity and short-term prognosis of ticagrelor in AMI patients undergoing emergency PCI during perioperative period. Int J Clin Exp Med. 2017;10(6):9595-600.

You J, Li H, Guo W, Li J, Gao L, Wang Y, et al. Platelet function testing guided antiplatelet therapy reduces cardiovascular events in Chinese patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention: The PATROL study. Catheter Cardiovasc Interv. 2020;95 Suppl 1:598-605. doi: 10.1002/ccd.28712.

Yudi MB, Clark DJ, Farouque O, Eccleston D, Andrianopoulos N, Duffy SJ, et al. Clopidogrel, prasugrel or ticagrelor in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Intern Med J. 2016;46(5):559-65. doi: 10.1111/imj.13041.

Yun JE, Kim YJ, Park JJ, Kim S, Park K, Cho MS, et al. Safety and Effectiveness of Contemporary P2Y12 Inhibitors in an East Asian Population With Acute Coronary Syndrome: A Nationwide Population-Based Cohort Study. J Am Heart Assoc. 2019;8(14):e012078. doi: 10.1161/JAHA.119.012078.

Yun KH, Rhee SJ, Ko JS. Comparison of the Infarct Size between the Loading of Ticagrelor and Clopidogrel in Patients with Acute Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Korean Circ J. 2017;47(5):705-13. doi: 10.4070/kcj.2017.0044.

Zhang Y, Zhao Y, Pang M, Wu Y, Zhuang K, Zhang H, et al. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. Acta Cardiol. 2016;71(3):309-16. doi: 10.2143/AC.71.3.3152091.

Zhao X, Ai G, Qiu M, Wang X, Zhang L, Yang X, et al. Efficacy of clopidogrel and ticagrelor under NT-proBNP in hospitalized ST-elevation acute coronary syndrome patients on percutaneous coronary intervention: CCC-ACS Project Analysis. Int J Cardiol. 2020;310:1-8. doi: 10.1016/j.ijcard.2020.04.004.

Zocca P, Van Der Heijden LC, Kok MM, Lowik MM, Hartmann M, Stoel MG, et al. Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT. EuroIntervention. 2017;13(10):1168-76. doi: 10.4244/EIJ-D-17-00634.

Systematic reviews, no appraisal done, only commented on:

Baldetti L, Melillo F, Moroni F, Gallone G, Pagnesi M, Venuti A, et al. Meta-Analysis Comparing P2Y12 Inhibitors in Acute Coronary Syndrome. Am J Cardio. 2020;125(12):1815-22. doi: http://dx.doi.org/10.1016/j.amjcard.2020.03.019.

Chen Q, Zhang Y, Wang Z, Wang S, Zhang H, Wang Y, et al. Efficacy and safety of low dose ticagrelor in patients with acute coronary syndrome: a systematic review and meta-analysis. Postgrad Med J. 2020. doi: 10.1136/postgradmedj-2019-137180.

Fan ZG, Zhang WL, Xu B, Ji J, Tian NL, He SH. Comparisons between ticagrelor and clopidogrel following percutaneous coronary intervention in patients with acute coronary syndrome: A comprehensive meta-analysis. Drug Des Devel Ther. 2019;13:719-30. doi: 10.2147/DDDT.S196535.

Galimzhanov AM, Azizov BS. Ticagrelor for Asian patients with acute coronary syndrome in real-world practice: A systematic review and meta-analysis of observational studies. Indian Heart J. 2019;71(1):15-24. doi: 10.1016/j.ihj.2019.01.003.

Guan W, Lu H, Yang K. Choosing between ticagrelor and clopidogrel following percutaneous coronary intervention: A systematic review and Meta-Analysis (2007-2017). Medicine (Baltimore). 2018;97(43):e12978. doi: 10.1097/MD.0000000000012978.

Kheiri B, Osman M, Abdalla A, Haykal T, Barbarawi M, Zayed Y, et al. Ticagrelor versus clopidogrel after fibrinolytic therapy in patients with ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized clinical trials. J Thromb Thrombolysis. 2018 Oct;46(3):299-303. doi: 10.1007/s11239-018-1706-2.

Li B, Jin X, Wang L, Cui L, Zhao Y, Meng B, et al. Loss of dominance of ticagrelor over clopidogrel in east asian patients with acute coronary syndrome. Int J Clin Exp Med. 2019;12(5):4528-39.

Misumida N, Aoi S, Kim SM, Ziada KM, Abdel-Latif A. Ticagrelor versus clopidogrel in East Asian patients with acute coronary syndrome: Systematic review and meta-analysis. Cardiovasc Revasc Med. 2018;19(6):689-694. doi: 10.1016/j.carrev.2018.01.009.

Montalto C, Morici N, Munafò AR, Mangieri A, Mandurino-Mirizzi A, D'Ascenzo F, et al. Optimal P2Y12 inhibition in older adults with acute coronary syndromes: A network meta-analysis of randomized controlled trials. Eur Heart J Cardiovasc Pharmacother. 2020:pvaa101. doi: 10.1093/ehjcvp/pvaa101.

Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, et al. Comparative Efficacy and Safety of Oral P2Y(12) Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. Circulation. 2020;142(2):150-60. doi: 10.1161/circulationaha.120.046786.

Wang D, Yang XH, Zhang JD, Li RB, Jia M, Cui XR. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: A meta-analysis. BMC Cardiovasc Disord. 2018;18(1):217. doi: 10.1186/s12872-018-0948-4.

Wu B, Lin H, Tobe RG, Zhang L, He B. Ticagrelor versus clopidogrel in East-Asian patients with acute coronary syndromes: A meta-analysis of randomized trials. J Comp Eff Res. 2018;7(3):281-291. doi: 10.2217/cer-2017-0074.

Wu H, Xiang X, Li D, Shen S, Li X. Efficacy and Safety of Ticagrelor Compared to Clopidogrel in Patients Undergoing Percutaneous Coronary Intervention: A Meta-Analysis. Curr Pharm Des. 2020. doi: 10.2174/1381612826666200614184007.

Excluded studies:

Ahn SG, Yoon J, Kim J, Uh Y, Kim KM, Lee JH, et al. Genotype- and Phenotype-Directed Personalization of Antiplatelet Treatment in Patients with Non-ST Elevation Acute Coronary Syndromes Undergoing Coronary Stenting. Korean Circ J. 2013;43(8):541-9. doi: 10.4070/kcj.2013.43.8.541.

Akerblom A, Wojdyla DM, Wallentin L, James SK, de Souza Brito F, Steg PG, et al. Ticagrelor in patients with heart failure after acute coronary syndromes-Insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2019;213:57-65.

Almendro-Delia M, García-Alcántara Á, de la Torre-Prados MV, Reina-Toral A, Arboleda-Sánchez JA, Butrón-Calderón M, et al. Safety and Efficacy of Prasugrel and Ticagrelor in Acute Coronary Syndrome. Results of a "Real World" Multicenter Registry. Rev Esp Cardiol (Engl Ed). 2017;70(11):952-959. doi: 10.1016/j.rec.2017.05.003.

Andell P, James S, Cannon C, Cyr D, Himmelmann A, Husted S, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and chronic obstructive pulmonary disease: an analysis from the platelet inhibition and patient outcomes (plato) trial. J Am Heart Assoc. 2015;4(10):e002490. doi: 10.1161/JAHA.115.002490.

Armstrong P, Siha H, Fu Y, Westerhout C, Steg P, James S, et al. ST-elevation acute coronary syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) trial: insights from the ECG substudy. Circulation. 2012;125(3):514-21. doi: 10.1161/CIRCULATIONAHA.111.047530.

Armstrong P, Westerhout C, Fu Y, Harrington R, Storey R, Katus H, et al. Quantitative ST-depression in acute coronary syndromes: the PLATO electrocardiographic substudy. Am J Med. 2013;126(8):723-729.e1. doi: 10.1016/j.amjmed.2013.01.038.

Becker R, Bass, J, Budaj A, Wojdyla D, James S, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011;32(23):2933-44. doi: 10.1093/eurheartj/ehr422.

Bellavia A, Wallentin L, Orsini N, James SK, Cannon CP, Himmelmann A, et al. Time-based measures of treatment effect: reassessment of ticagrelor and clopidogrel from the PLATO trial. Open Heart. 2017;4(2):e000557. doi: 10.1136/openhrt-2016-000557.

Berwanger O, Nicolau JC, Carvalho AC, Jiang L, Goodman SG, Nicholls SJ, et al. Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: A Randomized Clinical Trial. JAMA Cardiol. 2018;3(5):391-9. doi: 10.1001/jamacardio.2018.0612.

Brilakis E, Held C, Meier B, Cools F, Claeys M, Cornel J, et al. Effect of ticagrelor on the outcomes of patients with prior coronary artery bypass graft surgery: insights from the PLATelet inhibition and patient outcomes (PLATO) trial. Am Heart J. 2013;166(3):474-80. doi: 10.1016/j.ahj.2013.06.019.

Cannon C, Harrington R, James S, Ardissino D, Becker R, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010;375(9711):283-93. doi: 10.1016/S0140-6736(09)62191-7.

Chang-Zheng G. Comparison of the Effects of Ticagrelor and Clopidogrel on Inflammatory Factors, Vascular Endothelium Functions and Short-Term Prognosis in Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Emergency Percutaneous Coronary Intervention: a Pilot Study. Cell Physiol Biochem. 2018;48(1):385-396. doi: 10.1159/000491768.

Choi KN, Jin HY, Shin HC, Park YA, Seo JS, Jang JS, et al. Comparison of the Antiplatelet Effects of Once and Twice Daily Low-Dose Ticagrelor and Clopidogrel After Percutaneous Coronary Intervention. Am J Cardiol. 2017;120(2):201-6. doi: 10.1016/j.amjcard.2017.04.010.

Cornel J, Becker R, Goodman S, Husted S, Katus H, Santoso A, et al. Prior smoking status, clinical outcomes, and the comparison of ticagrelor with clopidogrel in acute coronary syndromes-insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2012;164(3):334-342.e1. doi: 10.1016/j.ahj.2012.06.005.

D'Ascenzo F, Biole C, Raposeiras-Roubin S, Gaido F, Abu-Assi E, Kinnaird T, et al. Average daily ischemic versus bleeding risk in patients with ACS undergoing PCI: Insights from the BleeMACS and RENAMI registries. Am Heart J. 2020;220:108-15. doi: https://dx.doi.org/10.1016/j.ahj.2019.10.001.

De Luca L, D'Ascenzo F, Musumeci G, Saia F, Parodi G, Varbella F, et al. Incidence and outcome of switching of oral platelet P2Y12 receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: The SCOPE registry. EuroIntervention. 2017;13(4):459-466. doi: 10.4244/EIJ-D-17-00092.

Deharo P, Quilici J, Camoin-Jau L, Johnson T, Bassez C, Bonnet G, et al. Benefit of Switching Dual Antiplatelet Therapy After Acute Coronary Syndrome According to On-Treatment Platelet Reactivity: the TOPIC-VASP Pre-Specified Analysis of the TOPIC Randomized Study. JACC Cardiovasc Interv. 2017;10(24):2560-2570. doi: 10.1016/j.jcin.2017.08.044.

Di Vito L, Versaci F, Limbruno U, Pawlowski T, Gatto L, Romagnoli E, et al. Impact of oral P2Y12 inhibitors on residual thrombus burden and reperfusion indexes in patients with ST-segment elevation myocardial infarction. J Cardiovasc Med (Hagerstown). 2016;17(9):701-6. doi: 10.2459/JCM.0000000000000392.

DiNicolantonio JJ, Serebruany VL. Exploring the ticagrelor-statin interplay in the PLATO trial. Cardiology. 2013;124(2):105-7. doi: 10.1159/000346151.

Dong P, Yang X, Bian S. Genetic Polymorphism of CYP2C19 and Inhibitory Effects of Ticagrelor and Clopidogrel Towards Post-Percutaneous Coronary Intervention (PCI) Platelet Aggregation in Patients with Acute Coronary Syndromes. Med Sci Monit. 2016;22:4929-4936. doi: 10.12659/msm.902120.

Franchi F, James SK, Ghukasyan Lakic T, Budaj AJ, Cornel JH, Katus HA, et al. Impact of Diabetes Mellitus and Chronic Kidney Disease on Cardiovascular Outcomes and Platelet P2Y12 Receptor Antagonist Effects in Patients With Acute Coronary Syndromes: Insights From the PLATO Trial. J Am Heart Assoc. 2019;8(6):e011139. doi: 10.1161/JAHA.118.011139.

Goodman S, Clare R, Pieper K, Nicolau J, Storey R, Cantor W, et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. Circulation. 2012;125(8):978-86. doi: 10.1161/CIRCULATIONAHA.111.032912.

Grodecki K, Huczek Z, Scislo P, Kowara M, Raposeiras-Roubin S, D'Ascenzo F, et al. Gender-related differences in post-discharge bleeding among patients with acute coronary syndrome on dual antiplatelet therapy: A BleeMACS sub-study. Thromb Res. 2018;168:156-163. doi: 10.1016/j.thromres.2018.06.022.

Hamilos M, Kanakakis J, Anastasiou I, Karvounis C, Vasilikos V, Goudevenos J, et al. Ticagrelor versus Clopidogrel in patients with STEMI treated with thrombolysis: the MIRTOS trial. EuroIntervention. 2020:EIJ-D-20-00268. doi: 10.4244/EIJ-D-20-00268.

Held C, Senblad N, Bass, J, Becker R, Cannon C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (platelet inhibition and patient outcomes) trial J Am Coll Cardiol. 2011;57(6):672-84. doi: 10.1016/j.jacc.2010.10.029

Husted S, Harrington R, Cannon C, Storey R, Mitchell P, Emanuelsson H. Bleeding risk with AZD6140, a reversible P2Y12 receptor antagonist, vs. clopidogrel in patients undergoing coronary artery bypass grafting in the DISPERSE2 trial. Int J Clin Pract. 2009;63(4):667-70. doi: 10.1111/j.1742-1241.2009.02030.x.

Husted S, James S, Bach R, Becker R, Budaj A, Heras M, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2014;35(23):1541-50. doi: 10.1093/eurheartj/ehu075.

Husted S, James S, Becker R, Horrow J, Katus H, Storey R, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes. 2012;5(5):680-8. doi: 10.1161/CIRCOUTCOMES.111.964395.

James S, Angiolillo D, Cornel J, Erlinge D, Husted S, Kontny F, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010;31(24):3006-16. doi: 10.1093/eurheartj/ehq325.

James S, Budaj A, Aylward P, Buck K, Cannon C, Cornel J, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2010;122(11):1056-67. doi: 10.1161/CIRCULATIONAHA.109.933796.

James S, Roe M, Cannon C, Cornel J, Horrow J, Husted S, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. BMJ. 2011;342:d3527. doi: 10.1136/bmj.d3527.

James S, Storey R, Khurmi N, Husted S, Keltai M, Mahaffey K, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. Circulation. 2012;125(23):2914-21. doi: 10.1161/CIRCULATIONAHA.111.082727.

Jeong YJ, Park K, Kim YD. Comparison between ticagrelor and clopidogrel on myocardial blood flow in patients with acute coronary syndrome, using 13 N-ammonia positron emission tomography. Am Heart J. 2020;222:121-130. doi: 10.1016/j.ahj.2020.01.013.

Kang H, Clare R, Gao R, Held C, Himmelmann A, James S, et al. Ticagrelor versus clopidogrel in Asian patients with acute coronary syndrome: a retrospective analysis from the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Am Heart J. 2015;169(6):899-905.e1. doi: 10.1016/j.ahj.2015.03.015.

Kohli P, Wallentin L, Reyes E, Horrow J, Husted S, Angiolillo D, et al. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO Study. Circulation. 2013;127(6):673-80. doi: 10.1161/CIRCULATIONAHA.112.124248.

Kotsia A, Brilakis E, Held C, Cannon C, Steg G, Meier B, et al. Extent of coronary artery disease and outcomes after ticagrelor administration in patients with an acute coronary syndrome: insights from the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J. 2014;168(1):68-75.e2. doi: 10.1016/j.ahj.2014.04.001.

Kunadian V, James S, Wojdyla D, Zorkun C, Wu J, Storey R, et al. Angiographic outcomes in the PLATO Trial (Platelet Inhibition and Patient Outcomes). JACC Cardiovasc Interv. 2013;6(7):671-83. doi: 10.1016/j.jcin.2013.03.014.

Li DT, Li SB, Zheng JY, Tang HH, Qiu YG, Xue N, et al. Analysis of Ticagrelor's Cardio-protective Effects on Patients with ST-segment Elevation Acute Coronary Syndrome Accompanied with Diabetes. Open Med (Wars). 2019;14:234-240. doi: 10.1515/med-2019-0017.

Li W, Guo S, Wang S, Sun X, Li Z, Sun X, et al. Comparison of Ticagrelor with Clopidogrel in Reducing Interleukin-17 and Myeloperoxidase Expression in Thrombus and Improving Postprocedural Coronary Flow in ST-segment Elevation Myocardial Infarction Patients. J Pharm Pharm Sci. 2018;21(1):207-216. doi: 10.18433/jpps29624.

Lindholm D, Varenhorst C, Cannon C, Harrington R, Himmelmann A, Maya J, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J. 2014;35(31):2083-93. doi: 10.1093/eurheartj/ehu160.

Lupu L, Shepshelovich D, Banai S, Hershkoviz R, Isakov O. Effect of Ticagrelor on Reducing the Risk of Gram-Positive Infections in Patients With Acute Coronary Syndrome. Am J Cardiol. 2020;130:56-63. doi: 10.1016/j.amjcard.2020.06.016.

Mahaffey K, Held C, Wojdyla D, James S, Katus H, Husted S, et al. Ticagrelor effects on myocardial infarction and the impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol. 2014;63(15):1493-9. doi: 10.1016/j.jacc.2014.01.038.

Mahaffey KW, Wojdyla DM, Carroll K, Becker RC, Storey RF, Angiolillo DJ, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial. Circulation. 2011;124(5):544-54. doi: 10.1161/CIRCULATIONAHA.111.04749

Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, et al. 1-Year Outcomes of Patients Undergoing Primary Angioplasty for Myocardial Infarction Treated With Prasugrel Versus Ticagrelor. J Am Coll Cardiol. 2018;71(4):371-381. doi: 10.1016/j.jacc.2017.11.008.

Musallam A, Orvin K, Perl L, Mosseri M, Arbel Y, Roguin A, et al. Effect of Modifying Antiplatelet Treatment to Ticagrelor in High-Risk Coronary Patients With Low Response to Clopidogrel (MATTIS). Can J Cardiol. 2016;32(10):1246.e13-1246.e19. doi: 10.1016/j.cjca.2015.11.023.

Oldgren J, Steg PG, Hohnloser SH, Lip GYH, Kimura T, Nordaby M, et al. Dabigatran dual therapy with ticagrelor or clopidogrel after percutaneous coronary intervention in atrial fibrillation patients with or without acute coronary syndrome: a subgroup analysis from the RE-DUAL PCI trial. Eur Heart J. 2019;40(19):1553-1562. doi: 10.1093/eurheartj/ehz059.

Patel M, Becker R, Wojdyla D, Emanuelsson H, Hiatt W, Horrow J, et al. Cardiovascular events in acute coronary syndrome patients with peripheral arterial disease treated with ticagrelor compared with clopidogrel: data from the PLATO Trial. Eur J Prev Cardiol. 2015;22(6):734-42. doi: 10.1177/2047487314533215.

Pollack C, Davoudi F, Diercks D, Becker R, James S, Lim S, et al. Relative efficacy and safety of ticagelor vs clopidogrel as a function of time to invasive management in non-ST-segment elevation acute coronary syndrome in the PLATO trial. Clin Cardiol. 2017;40(6):390-398. doi: 10.1002/clc.22733.

Ren Q, Ren C, Liu X, Dong C, Zhang X. Ticagrelor vs. clopidogrel in non-ST-elevation acute coronary syndromes. Herz. 2016;41(3):246-9. doi: 10.1007/s00059-015-4359-3.

Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, et al. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. Eur Heart J. 2020. doi: 10.1093/eurheartj/ehz917.

Scirica B, Bansilal S, Davoudi F, Armstrong P, Clare R, Schulte P, et al. Safety of ticagrelor in patients with baseline conduction abnormalities: a PLATO (Study of Platelet Inhibition and Patient Outcomes) analysis. Am Heart J. 2018;202:54-60. doi: 10.1016/j.ahj.2018.04.020.

Scirica BM, Cannon CP, Emanuelsson H, Michelson EL, Harrington RA, Husted S, et al. The incidence of bradyarrhythmias and clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial: results of the continuous electrocardiographic assessment substudy. J Am Coll Cardiol. 2011;57(19):1908-16. doi: 10.1016/j.jacc.2010.11.056.

Steg P, James S, Harrington R, Ardissino D, Becker R, Cannon C, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010;122(21):2131-41. doi: 10.1161/CIRCULATIONAHA.109.927582.

Steg PG, Harrington RA, Emanuelsson H, Katus HA, Mahaffey KW, Meier B, et al. Stent thrombosis with ticagrelor versus clopidogrel in patients with acute coronary syndromes: an analysis from the prospective, randomized PLATO trial. Circulation. 2013;128(10):1055-65. doi: 10.1161/CIRCULATIONAHA.113.002589.

Storey R, Angiolillo D, Patil S, Desai B, Ecob R, Husted S, et al. Inhibitory effects of ticagrelor compared with clopidogrel on platelet function in patients with acute coronary syndromes: the PLATO (PLATelet inhibition and patient Outcomes) PLATELET substudy. J Am Coll Cardiol. 2010;56(18):1456-62. doi: 10.1016/j.jacc.2010.03.100.

Storey R, Becker R, Harrington R, Husted S, James S, Cools F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J. 2011a;32(23):2945-53. doi: 10.1093/eurheartj/ehr231.

Storey R, Husted S, Harrington R, Heptinstall S, Wilcox R, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol. 2007;50(19):1852-6. doi: 10.1016/j.jacc.2007.07.058.

Storey R, James S, Siegbahn A, Varenhorst C, Held C, Ycas J, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. Platelets. 2014;25(7):517-25. doi: 10.3109/09537104.2013.842965.

Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, et al. Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the platelet inhibition and patient outcomes [PLATO] pulmonary function substudy). Am J Cardiol. 2011b;108(11):1542-6. doi: 10.1016/j.amjcard.2011.07.015.

Sukul D, Seth M, Dixon SR, Kh, elwal A, Lalonde TA, et al. Contemporary Trends and Outcomes Associated with the Preprocedural Use of Oral P2Y12 Inhibitors in Patients Undergoing Percutaneous Coronary Intervention: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). J Invasive Cardiol. 2017;29(10):340-351.

Thomas MR, James SK, Becker RC, Himmelmann A, Katus HA, Cannon CP, et al. Prognostic impact of baseline inflammatory markers in patients with acute coronary syndromes treated with ticagrelor and clopidogrel. Eur Heart J Acute Cardiovasc Care. 2019:2048872619878075. doi: 10.1177/2048872619878075.

Wallentin L, Lindholm D, Siegbahn A, Wernroth L, Becker R, Cannon C, et al. Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2014;129(3):293-303. doi: 10.1161/CIRCULATIONAHA.113.004420.

Varenhorst C, Alström U, Braun O, Storey R, Mahaffey K, Bertilsson M, et al. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. Heart. 2014;100(22):1762-9. doi: 10.1136/heartjnl-2014-305619.

Varenhorst C, Alström U, Scirica B, Hogue C, Åsenblad N, Storey R, et al. Factors contributing to the lower mortality with ticagrelor compared with clopidogrel in patients undergoing coronary artery bypass surgery. J Am Coll Cardiol. 2012;60(17):1623-30. doi: 10.1016/j.jacc.2012.07.0.

Velders M, Abtan J, Angiolillo D, Ardissino D, Harrington R, Hellkamp A, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. Heart. 2016;102(8):617-25. doi: 10.1136/heartjnl-2015-308963.

Xue J, Li M, Wang L, Ma M, Zhang J. Comparison of the efficacy of half ticagrelor loading doses and clopidogrel in elderly acute coronary syndrome patients in China. Trop J Pharm Res. 2020;19(3):661-6. doi: 10.4314/tjpr.v19i3.29.

Yang Y, Zhang W, Li P, Gu Y, Ma L, Fan M. Association of CYP2C19*2 polymorphisms and high on-treatment platelet reactivity in acute myocardial infarction or coronary artery in-stent restenosis patients during dual antiplatelet therapy. Med Drug Discov. 2020;6. doi: 10.1016/j.medidd.2020.100038.

Yao G, Su G, Li K, Li B, Dong H. Comparative study of ticagrelor and clopidogrel in therapeutic effect of acute myocardial infarction patients undergoing percutaneous coronary intervention. Saudi J Biol Sci. 2017;24(8):1818-1820. doi: 10.1016/j.sjbs.2017.11.020.

Zhang D, Song X, Chen Y, Raposeiras-Roubin S, Abu-Assi E, Henriques JPS, et al. Outcome of Patients With Prior Stroke/Transient Ischemic Attack and Acute Coronary Syndromes. Angiology. 2020;71(4):324-32. doi: http://dx.doi.org/10.1177/0003319719889524.

Zhao G, Zhou M, Ma C, Huo Y, Smith SC, Jr., Fonarow GC, et al. In-Hospital Outcomes of Dual Loading Antiplatelet Therapy in Patients 75 Years and Older With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: Findings From the CCC-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) Project. J Am Heart Assoc. 2018;7(7):e008100. doi: 10.1161/JAHA.117.008100.

Zhu K, Fu Q, Zhang N, Huang YJ, Zhang Q. Pre-PCI medication using clopidogrel and ticagrelor in the treatment of patients with acute myocardial infarction. Eur Rev Med Pharmacol Sci. 2015;19(23):4636-41.

Other references:

Angiolillo DJ, Rollini F, Storey RF, Bhatt DL, James S, Schneider DJ, et al. International Expert Consensus on Switching Platelet P2Y12 Receptor-Inhibiting Therapies. Circulation. 2017;136(20):1955-1975. doi: 10.1161/CIRCULATIONAHA.117.031164.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. doi: 10.1136/bmj.328.7454.1490.

Burke AP, Kolodgie FD, Farb A, Weber DK, Malcom GT, Smialek J. Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression. Circulation. 2001;103(7):934-40. doi: 10.1161/01.cir.103.7.934.

[Checklist from SBU regarding cohort studies. (Modified) Version 2014]. [Internet]. [cited 2020 Jan 24] Available from: https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/ede81730-12c9-4917-bac9-3a0abb1268c1/Granskningsmall%20kohortstudier%20med%20kontrollgrupp.pdf?a=false&guest=true

[Checklist from SBU regarding observational studies]. [Internet]. [cited 2020 Jan 24] Available from: https://www.sbu.se/globalassets/ebm/bedomning_icke_randomiserade_studier_fullfolja.pdf

[Checklist from SBU regarding randomized controlled trials]. (Modified) Version 2014]. [Internet]. [cited 2020 Jan 24] Available from: https://alfresco.vgregion.se/alfresco/service/vgr/storage/node/content/workspace/SpacesStore/122d27a7-a872-4932-8bac-378d1c3ecd34/Granskningsmall%20randomiserad%20kontrollerad%20pr%c3%b6vning%20RCT.pdf?a=false&guest=true

[Checklist from SBU regarding randomized controlled trials]. [Internet]. [cited 2020 Jan 24]. Available from: https://www.sbu.se/globalassets/ebm/bedomning_randomiserade_studier_fullfolja.pdf

Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, et al.; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet. 2017 ;389(10073):1025-1034. doi: 10.1016/S0140-6736(17)30397-5.

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127(1):143-52. doi: 10.1161/CIR.0b013e318282ab8f.

GRADE Working Group. [Internet]. [Place unknown]: GRADE Working Group, c200-2017 [cited 2017 Feb 13]. Available from: http://www.gradeworkinggroup.org

Henriksson M, Nikolic E, Ohna A, Wallentin L, Janzon M. Ticagrelor treatment in patients with acute coronary syndrome is cost-effective in Sweden and Denmark. Scand Cardiovasc J. 2014;48(3):138-47. doi: 10.3109/14017431.2014.902494.

Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J. 2006;27(9):1038-47. doi: 10.1093/eurheartj/ehi754.

Husted S, James S, Becker R, Horrow J, Katus H, Storey R, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes: a substudy from the prospective randomized PLATelet inhibition and patient Outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes. 2012;5(5):680-8. doi: 10.1161/CIRCOUTCOMES.111.964395.

Janzon M, James S, Cannon CP, Storey RF, Mellström C, Nicolau JC, et al. Health economic analysis of ticagrelor in patients with acute coronary syndromes intended for non-invasive therapy. Heart. 2015;101(2):119-25. doi: 10.1136/heartjnl-2014-305864.

Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, et al. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. Eur Heart J. 2006;27(10):1166-73. doi: 10.1093/eurheartj/ehi877.

Lindholm D, Varenhorst C, Cannon C, Harrington R, Himmelmann A, Maya J, et al. Ticagrelor vs. clopidogrel in patients with non-ST-elevation acute coronary syndrome with or without revascularization: results from the PLATO trial. Eur Heart J. 2014;35(31):2083-93. doi: 10.1093/eurheartj/ehu160.

Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736-47. doi: 10.1161/circulationaha.110.009449.

Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.

Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part II. Circulation. 2003;108(15):1772-8. doi: 10.1161/01.cir.0000087481.55887.c9.

Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE Jr., Messenger JC, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. Lancet. 2015;385(9973):1114-22. doi: 10.1016/s0140-6736(14)61932-2.

Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40(2):87-165. doi: 10.1093/eurheartj/ehy394.

Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC, et al. Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis. J Am Coll Cardiol. 2015 Jun 16;65(23):2496-507. doi: 10.1016/j.jacc.2015.04.017. PMID: 26065988.

REKlistan. Läkemedelskommittén i Västra Götalandsregionen [Internet]. [cited 2021 May 19]. Available from: https://reklistan.vgregion.se/

Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol. 2007;50(19):1852-6. doi: 10.1016/j.jacc.2007.07.058

Svensson M, Nilsson FO, Arnberg K. Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness. Pharmacoeconomics. 2015;33(11):1229-36. doi: 10.1007/s40273-015-0307-6.

Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2006;113(6):e85-151. doi: 10.1161/circulationaha.105.171600.

Tillberg M, editor. Swedeheart Annual Report 2019 [Internet]. Stockholm: Danderyd Hospital; 2020. [cited 2020 Oct 21]. Available from: https://www.ucr.uu.se/swedeheart/dokument-sh/arsrapporter-sh/1-swedeheart-annual-report-2019

Wallentin L, Lindhagen L, Ärnström E, Husted S, Janzon M, Johnsen SP, et al. Early invasive versus non-invasive treatment in patients with non-ST-elevation acute coronary syndrome (FRISC-II): 15 year follow-up of a prospective, randomised, multicentre study. Lancet. 2016 Oct 15;388(10054):1903-1911. doi: 10.1016/S0140-6736(16)31276-4. Epub 2016 Aug 29. PMID: 27585757.

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Ahn 2020 South Korea	nRCT Cohort	2 years	PS-matched I: 787 C: 787	AMI with multivessel disease	I: 64 C:64	I: 77% C: 78%	Mortality MI Bleeding Stent thrombosis
Alexopoulos 2015 Greece	RCT Open-label	In hospital	I: 28 (high dose clopidogrel) C: 28	STEMI with high platelet reactivity	I: 62 C: 59	C: 82% I: 89%	Mortality MI Bleeding Stent thrombosis
Alexopoulos 2016 Greece	nRCT Cohort	1 year	I: 959 C: 717	ACS with PCI	I: 65 C: 60	I: 78% C: 85%	Mortality MI Bleeding Stent thrombosis (urgent revascularisation)
Alexopoulos 2017 Greece	nRCT Cohort	1 year	I: 762 C: 738	ACS with PCI Patients not likely to come to follow up excluded	I: NR C: 60	I: NR C: 84%	Dyspnea
Angiolillo 2016 USA	RCT Open-label	14 days	I: 49 C: 51	Troponin-negative ACS with ad hoc PCI	I: 63 C: 60	I: 74% C: 67%	Mortality Bleeding Angina Dyspnea
Antoniou 2018 UK	nRCT Cohort	Median: 1.8 years	I: 520 C: 1,203	ACS with PCI	67	73%	Bleeding
Berwanger 2019 Multi-centre: Argentina, Australia, Brazil Canada, China, Comombia, New Zealand, Peru, Russia,Ukraine	RCT Single-blind (adjudicated endpoints)	1 year	I: 1,886 C: 1,913	STEMI, post-fibrinolytic therapy, <75 years of age	59	77%	Mortality MI Bleeding Dyspnea

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Blin 2019 France	nRCT Cohort	1 year	PS-matched I: 9,224 C: 9,224	Patients with first ACS and alive at discharge and not transferred to a rehabilitation centre.	I: 67 C: 67	73.5%	Mortality Bleeding
Brener 2019 US	nRCT Cohort	1 year	I: 774 C: 665	ACS with PCI	66	60%	Mortality MI Bleeding
Cannon 2007 Multi-centre: 14 countries	RCT Double-blind	12 weeks	I: 327 C: 334	NSTEMI Patient recruitment 2004-2005	I: 62 C: 64	63%	Mortality MI Bleeding Dyspnea
Cao 2019 China	RCT Open-label	30 days	I: 48 C: 49	STEMI	I: 63 C: 62	I: 61% C: 61%	Mortality MI Bleeding Stent thrombosis Dyspnea
Chang 2020 Taiwan	nRCT Cohort	9 months	I: 22,385 C: 10,057	AMI	≥75 years I: 36% C: 20% After PS weighting: 20%	I: 70% C: 80% After PS weighting: 79%/80%	Mortality MI Bleeding
Choe 2019 South Korea	nRCT Cohort	Median: 468 days	PS-matched I: 1,203 C: 1,203	ACS with PCI	67	71%	Mortality MI Bleeding
De Filippo 2019 Multi-centre: Europe, Asia, North and South America	nRCT Cohort	Median: 1 year	*eGFR >60* I: 11,803 C: 2,809 *eGFR <60* I: 1,758 C: 540	ACS stratified by eGFR	*eGFR >60* 62 *eGFR <60* 73	*eGFR >60* 80% *eGFR <60* 57%	Mortality MI Bleeding

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Dehghani 2017 Canada	RCT Open-label	30 days	I: 68 C: 76	STEMI, post-fibrinolytic therapy	I: 64 C: 62	I: 72% C: 76%	Mortality MI Bleeding Rehospitalisation Dyspnea
Edfors 2018 Sweden	nRCT Cohort	1 year	*eGFR >60* I: 24,130 C: 9,538 *eGFR 30-60* I: 7,817 C: 1,986 *eGFR<30* I: 1,525 C: 210	ACS stratified by eGFR	*eGFR >60* I: 67 C: 65 *eGFR 30-60* I: 81 C: 77 *eGFR<30* I: 80 C: 78	*eGFR >60* I: 69% C: 74% *eGFR 30-60* I: 55% C: 59% *eGFR<30* I: 56% C: 56%	Mortality MI Bleeding
Gajanana 2018 US	nRCT Cohort	In hospital	I: 1,722 C: 861	ACS	I: 66 C: 62	I: 64% C: 67%	MI Bleeding Stent thrombosis
Gasecka 2020 Poland	RCT Open-label (for clinical data)	6 months	I: 30 C: 30	AMI with PCI	I: 63 C: 66	I: 75% C: 70%	Mortality MI Bleeding Stent thrombosis Rehospitalisation
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	12 months	I: 500 C: 502	NSTE-ACS, ≥70 years	77	I: 63% C: 65%	Mortality MI Bleeding Stent thrombosis

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Giordana 2016 Multi-centre Europe: Spain, Holland, Greece, Germany, Italy, Poland East Asia: China Japan	nRCT Cohort	12 months	Europe: I: 8,612 C: 464 East Asia I: 2,132 C: 136	ACS with PCI	Europe: 65 East Asia: 62	Europe: 77% East Asia: 78%	Mortality MI Bleeding
Gosling 2017 UK	nRCT Cohort	12 months	I: 4,653 C: 4,917	ACS	64	70%	Mortality Stent thrombosis
Goto 2015 Multi-centre. Japan, Taiwan, South Korea	RCT Double-blind	12 months	I: 400 C: 401	ACS planned for PCI	67	77%	Mortality MI Bleeding Dyspnea
Grimaldi-Bensouda 2018 France	nRCT Case-control	Medication 30 days prior to index date	1,047 cases with recurrent MI 2,234 matched controls without recurrent MI	ACS	71	71%	MI
Gu 2017 China	RCT Open-label	3 months	I: 36 (high-dose clopidogrel) C: 38 (standard dose)	NSTEMI with inadequate response to clopidogrel (reduction of PAR <30% or PAR >70%).	I: 60 C: 59	I: 75% C: 79%	Mortality MI Bleeding Rehospitalisation Dyspnea
Hansson 2016 Sweden	nRCT Cohort	In hospital (for mortality 30 days)	I: 978 C: 1,266	ACS with CABG	68	79%	Mortality Bleeding
Jing 2016 China	RCT Open-label	In hospital	I: 94 C: 94	STEMI planned for PCI	I: 55 C: 59	I: 62% C: 57%	Mortality Bleeding

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Kang 2017 South Korea	nRCT Cohort	1 year	I: 6,411 C: 1,708	ACS but not CABG	I: 65 C: 63	I: 72% C: 77%	Mortality MI Bleeding (PS-matched analysis) Stent thrombosis
Kim 2017 US	nRCT Cohort	1 year	PS-matched I: 9,505 C: 2,376	ACS with PCI	I: 58 C: 59	I: 79% C: 75%	MI Rehospitalisation
Kim 2018 South Korea	RCT Open label	3 months	I: 57 C: 58	AMI with PCI and stent implantation	I: 62 C: 60	I: 85% C: 81%	Stent thrombosis
Kim 2019 South Korea	nRCT Cohort	1 year	I: 15,459 C: 4,811	ACS with PCI	I: 60 C: 57	I: 81% C: 86%	Mortality MI Bleeding
Krackhardt 2020 Germany	nRCT Cohort	9-12 months	I: 1,549 C: 1,020	ACS	I: 68 C: 64	I: 71% C:78%	Mortality MI Bleeding Stent thrombosis
Krishnamurthy 2019 UK	nRCT Cohort	1 year	I: 1,648 C: 811	STEMI with PCI	I: 65 C: 63	72%	Mortality MI Bleeding
Lee 2018 Taiwan	nRCT Cohort	18 months	PS-matched I: 19,112 C: 2,389	AMI who survived more than 30 days after the event	I: 64 C: 60	I: 67% C: 84%	Mortality MI Bleeding
Levin 2013 Multi-centre: Sub-study to PLATO trial	RCT Double-blind	12 months	I: 8,384 C: 8,462	ACS	62	72%	HRQL
Li 2015 China	RCT Single-blind	6 months	I: 24 (high dose clopidogrel) C: 24 (standard dose)	STEMI/NSTEMI/in-stent restenosis with high on-treatment platelet reactivity	I: 65 C: 68	67%	Mortality MI Bleeding Dyspnea

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Li 2018 China	RCT Open-label	1 year	I: 324 C: 329 In analysis: I: 281 C: 161	STEMI with PCI Analysis based on patients without switch	I: 63 C: 60	I: 75% C: 84%	Mortality MI Bleeding Rehospitalisation Stent thrombosis Angina
Liu 2017 China	RCT Double-blind	30 days	I: 87 C: 86	STEMI with PCI, diabetes	I: 58 C: 59	I: 60% C: 73%	Mortality MI Bleeding Stent thrombosis
Liu 2019a China	RCT Open-label	30 days	I: 40 (high-dose clopidogrel) C: 40 (half-dose ticagrelor)	ACS and high on-treatment platelet reactivity	I: 59 C: 62	I: 69% C: 55%	Mortality MI Bleeding Stent thrombosis Dyspnea
Liu 2019b China	RCT Open-label	1 year	I: 100 C: 108	STEMI, diabetes	I: 69 C: 68	I: 58 C: 54	Mortality MI Bleeding
Lu 2016 China	RCT Open-label	1 year	I: 108 C: 95	ACS (NYHA III and IV excluded) after PCI	I: 60 C: 59	I: 56% C: 55%	Mortality MI Bleeding Stent thrombosis Angina Dyspnea
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	1 year	I: 472 C: 471	ACS	I: 48 C: 50	I: 64% C: 68%	Mortality MI Bleeding Stent thrombosis
Ohman 2017 Multi-centre: 21 countries	nRCT (RCT: rivaroxaban versus aspirin)	1 year	I: 666 C: 852	ACS For those <55years of age: diabetes or previous MI required	63	I: 72% C: 78%	Mortality MI Bleeding Stent thrombosis

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Olier 2018 UK	nRCT Cohort	1 year	I: 58,248 C: 13,105	STEMI and PCI	I: 64 C: 63	I: 73% C: 74%	Mortality Bleeding
Orenes-Pinero 2019 Spanien	nRCT Cohort	1 year	I: NR C: NR I & C: 1,717	ACS, without switching of medication during hospitalisation	NR	71%	Mortality
Park 2016 South Korea	nRCT Cohort	6 months	PS matched I: 1,377 C: 1,377	AMI with successful PCI	I: 62 C: 62	I: 79% C: 78%	Mortality MI Bleeding Stent thrombosis
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	12 months	I: 400 C: 400	ACS	I: 62 C: 63	I: 76% C: 74%	Mortality MI Bleeding Stent thrombosis Dyspnea
Park 2019b South Korea	RCT Open-label	6 months	I: 60 C: 60	ACS with PCI	I: 59 C: 57	I: 73% C: 77%	Mortality Bleeding Stent thrombosis Dyspnea
Peyracchia 2020 Multi-centre: European countries and Japan, China, Canada and Brazil	nRCT	12 months	PS-matched I: 1,831 C: 798	ACS with PCI	I: 61 C: 60	I: 82% C:83%	Mortality MI Bleeding
Rasia 2017 Italy	nRCT Cohort	12 months	I: 135 (Plavix), 1,321 (clopidogrel) C: 599	ACS with PCI	I: Plavix: 71, clopidogrel: 70 C: 64	I: Plavix: 73% clopidogrel: 71% C: 64%	Mortality MI Bleeding Stent thrombosis

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Sahlen 2016 Sweden	nRCT Cohort	24 months	I: 33,119 C: 11,954	AMI	I: 71 C: 67	I: 65% C: 72%	Mortality MI Bleeding
Schmucker 2019 Germany	nRCT Cohort	1 year	I: 552 C: 535 PS-matched I: 238 C: 238	STEMI, ≥75 years	I: 81 C: 81 PS-matched NR	I: 49% C: 50% PS-matched I: 52% C: 49%	Mortality MI Bleeding
Sheikh Rezaei 2017 Austria	nRCT Cohort	Median: 25 months	I: 18,640 C: 7,507	ACS	Median I: 71 C: 65	I: 61% C: 69%	Mortality
Sim 2018 South Korea	nRCT Cohort	1 year	PS-matched I: 1,553 C: 1,533	AMI with PCI and DES	I: 63 C: 62	I: 78% C: 79%	Mortality MI Bleeding Stent thrombosis
Sim 2019 South Korea	nRCT Cohort	12 months	I: 3,180 C: 659	NSTEMI with PCI and DES	I: 66 C: 62	I: 89% C: 78%	Mortality MI Bleeding Stent thrombosis
Spoendlin 2018 US	nRCT Cohort	1 year	PS-matched I: 3,013 C: 3,013	ACS, diabetes	61	69%	Bleeding
Sun 2019 China	nRCT Cohort	12 months	I: 1,833 C: 1,833	ACS with PCI	60	I: 74% C: 75%	Mortality MI Bleeding
Szummer 2020 Sweden	nRCT Cohort	12 months	*≥80 years* I: 8,434 C: 5,571 *<80 years* I: 22,415 C: 36,256	AMI	After IPTW *≥80 years* 85 *<80 years* 64	After IPTW *≥80 years* 49% *<80 years* 28%	Mortality MI Bleeding

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Tang 2016 China	RCT Open-label	6 months	I: 210 C: 210	STEMI with PCI	64	I: 73% C: 71%	Mortality MI Bleeding Stent thrombosis
Turgeon 2020 Canada	nRCT Cohort	12 months	PS-matched I: 3,711 C: 3,711	ACS with PCI	Median: 61	I: 76% C: 77%	Mortality MI (ACS) Bleeding Stent thrombosis Dyspnea
Wallentin 2009 Multi-centre: 43 countries PLATO trial	RCT Double-blind	1 year	I: 9,291 C: 9,333	ACS	Median: 62	72%	Mortality MI Bleeding Stent thrombosis Dyspnea
Wang 2016a China	RCT Double-blind	1 year	I: 100 C: 100	ACS, >65 years	I: 80 C: 79	I: 66% C: 69%	Mortality MI Bleeding
Wang 2016b China	RCT Open-label	30 days	I: 87 C: 87	STEMI, dementia, 60-80 years of age	≈70	I: 57% C: 55%	Mortality MI Stent thrombosis Dyspnea
Wang 2018 China	nRCT Cohort	1 year	PS-matched I: 1,559 C: 779	ACS with PCI	I: 61 C: 61	I: 72% C: 71%	Mortality MI Bleeding
Wang 2019 China	RCT Open-label	6 months	I: 148 C: 150	STEMI	I: 60 C: 61	I: 82% C: 77%	Mortality MI Bleeding
Welsh 2019 Multi-centre: 20 countries (TOTAL trial)	nRCT Cohort	1 year	I: 6,500 C: 2,188	STEMI	NR	I: 76% C: 78%	Mortality MI Bleeding Stent thrombosis Rehospitalisation

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Wu 2018 China	RCT Open-label	1 year	I: 120 C: 124	AMI with emergency PCI	I: 61 C: 59	I: 78% C: 79%	Mortality MI Bleeding Stent thrombosis Angina Dyspnea
Vyas 2017 US	nRCT Cohort	1 year	I: 7,283 C: 1,049	ACS	I: 59 C: 56	I: 73% C: 78%	Bleeding Rehospitalisation Dyspnea
Völz 2020 Sweden	nRCT Cohort	12 months	I: 12,168 C: 2,929	ACS	67	I: 72% C: 73%	Mortality Bleeding Stent thrombosis
Xin 2019 China	nRCT Cohort	2 years	I: 560 (unclear clopidogrel dose) C: 523	Recurrent ACS with PCI	I: 67 C: 66	I: 52% C: 49%	Mortality MI Bleeding Stent thrombosis Angina HRQL
Xiong 2015 China	RCT Open-label	30 days	I: 112 (unclear dose including both standard and high dose) C: 112	ACS with non-emergent PCI, CYP2C19 poor metabolisers; unclear dosing of clopidogrel	I: 67 C: 68	I: 71% C: 70%	Mortality MI Bleeding
Xue 2016 China	RCT Double-blind	In hospital	I: 25 C: 25	NSTEMI	I: 60 C: 61	I: 70% C: 48%	Bleeding Dyspnea
Yan 2016 Multi-centre: 11 countries	nRCT Cohort	1 year	*With PPI* I: 4814 C: 351 *Without PPI* I: 4126 C: 138	ACS	64	77%	Mortality MI Bleeding

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Yang 2018 China	RCT Open-label	6 months	I: 60 C: 60	AMI with emergent PCI	NR	NR	Mortality MI Bleeding Rehospitalisation
Yang 2020 China	RCT Open-label	12 months	I: 100 C: 100	ACS	I: 59 C :61	I: 55% C: 57%	Mortality
Yao 2017 China	RCT Open-label	6 months	I: 60 C: 60	AMI with PCI	I: 60 C: 60	I: 36% C: 38 %	Mortality MI Bleeding Angina
You 2020 China	RCT Open-label	1 year	I: 195 C: 105	STEMI, HPR (subgroup relevant for this HTA)	I: 69 C: 66	I:60% C:73%	Mortality MI Bleeding Stent thrombosis
Yudi 2016 Australia	nRCT Cohort	30 days and 1 year	I: 956 C: 526	ACS with PCI	I: 68 C: 62	I: 72% C: 78%	Mortality MI Bleeding
Yun 2017 South Korea	RCT Open-label	In hospital	C: 97 I: 97	STEMI with PCI	I: 64 C: 61	I: 74% C: 80%	Mortality
Yun 2019 South Korea	nRCT Cohort	Median: 18 months	PS-matched I: 11,402 C: 11,402	ACS	I: 61 C: 61	I: 79% C: 78%	Mortality MI Bleeding
Zhang 2016 China	RCT Open-label	6 months	I: 90 (High dose clopidogrel for 7 days, then standard dose) C: 91	ACS with PCI, CYP2C19 poor/intermediate metabolisers	I: 72 C: 69	I: 54% C: 46%	Mortality MI Bleeding Stent thrombosis Dyspnea

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 2 Characteristics of included studies, alphabetical order by the first author

First author Year Country	Study design	Length of follow-up	Study Groups; Intervention (clopidogrel) vs control (ticagrelor)	Patient group	Age, years (mean)	Men (Percentage)	Outcome variables
Zhao 2020 China	nRCT Cohort	During hospitalisation, within 15 days	8,520 C: 2,992	STEMI	I: 62 C: 60 (NR in NT-proBNP groups)	I: 80% C: 79% (NR in NT-proBNP groups)	Mortality MI Bleeding Stent thrombosis
Zocca 2017 Netherlands	nRCT Historic control	1 year	I: 1,009 C: 1,053	ACS with PCI and DES	I: 63 C: 64	I: 70% C: 71%	Mortality MI Bleeding Stent thrombosis

ACS = acute coronary syndrome, AMI = acute myocardial infarction, C = comparison, CABG = coronary artery by-pass grafting, eGFR = estimated glomerular filtration rate, HPR = high platelet reactivity, HRQL = health-related quality of life, HTA = health technology assessment, I = intervention, IPTW = inverse probability treatment weights, MI = myocardial infarction, NR = not reported, nRCT = non-randomised controlled trial, NSTE-ACS = non-ST-elevation acute coronary syndrome, NSTEMI = non-ST elevation myocardial infarction, PAR = platelet aggregation rate, PCI = percutaneous coronary intervention, PS = propensity score, RCT = randomised controlled trial, STEMI = ST elevation myocardial infarction, UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 3 Excluded articles

Author year	Reason for exclusion
Ahn 2013	RCT, but cohort study according to our PICO. Too few patients, <500 patients per group
Akerblom 2019	PLATO duplicate
Almendro-Delia 2017	Wrong C: ticagrelol/prasugrel
Andell 2015	PLATO duplicate
Armstrong 2012	PLATO duplicate
Armstrong 2013	PLATO duplicate
Becker 2011	PLATO duplicate
Bellavia 2017	PLATO duplicate
Berwanger 2018	Duplicate to Berwanger 2019
Brilakis 2013	PLATO duplicate
Cannon 2010	PLATO duplicate
Chang-Zheng 2018	Wrong I and C: ASA not mentioned to be used during the study
Choi 2017	Wrong P: ACS not mentioned, indication DAPT not mentioned
Cornel 2012	PLATO duplicate
D'Ascenzo 2020	Wrong O: ischemic and bleeding risk combined
De Luca 2017	Wrong I: clopidogrel/ticlopidin. Wrong C: ticagrelol/prasugrel
Deharo 2017	Wrong C: ticagrelol/prasugrel
Di Vito 2016	RCT, but cohort study according to our PICO. Too few patients, <500 patients per group
DiNicolantonio 2013	Wrong publication type: editorial
Dong 2016	Wrong I and C: ASA not mentioned to be used during the study
Franchi 2019	PLATO duplicate
Goodman 2012	PLATO duplicate
Grodecki 2018	Wrong C: ticagrelor/prasugrel
Hamilos 2020	Information regarding allocation to I/C missing for relevant outcomes
Held 2011	PLATO duplicate
Husted 2009	Wrong I and wrong C: Withdrawal of therapy
Husted 2012	PLATO duplicate
Husted 2014	PLATO duplicate
James 2010	PLATO duplicate
James 2010	PLATO duplicate
James 2011	PLATO duplicate
James 2012	PLATO duplicate

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 3 Excluded articles

Author year	Reason for exclusion
Jeong 2020	PLEIO duplicate (Park 2019 Comparison…)
Kang 2015	PLATO duplicate
Kohli 2013	PLATO duplicate
Kotsia 2014	PLATO duplicate
Kunadian 2013	Wrong O: angiographic outcome
Li 2018	Wrong O: biomarkers
Li 2019	Wrong C and I: ASA not mentioned to be used during the study
Lindholm 2014	PLATO duplicate
Lupu 2020	Restricted O: rehospitalisation due to Gram-positive infection
Mahaffey 2011	PLATO duplicate
Mahaffey 2014	PLATO duplicate
Motovska 2018	Wrong I: clopidogrel missing in RCT. After switch, too few patients for cohort study <500
Musallam 2016	Wrong P: stable angina included and not differentiated
Oldgren 2019	Wrong I and C: not ASA in all patients. Wrong P: stable patients mixed with ACS
Patel 2015	PLATO duplicate
Pollack 2017	PLATO duplicate
Ren 2016	Wrong O: outcome only presented as composite endpoint
Schnorbus 2020	Information regarding allocation to I/C missing for relevant outcomes
Scirica 2011	PLATO duplicate
Scirica 2018	Wrong O: outcome arrhythmic events
Steg 2010	PLATO duplicate
Steg 2013	PLATO duplicate
Storey 2007	Wrong O: platelet aggregation
Storey 2010	PLATO duplicate
Storey 2011a	PLATO duplicate
Storey 2011b	Wrong O: pulmonary function
Storey 2014	PLATO duplicate
Sukul 2017	Wrong P: mixed population unstable and stable angina
Thomas 2019	PLATO duplicate
Wallentin 2014	PLATO duplicate
Varenhorst 2012	PLATO duplicate
Varenhorst 2014	PLATO duplicate

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 3 Excluded articles

Author year	Reason for exclusion
Velders 2016	PLATO duplicate
Xue 2020	Wrong O: outcome only presented as composite endpoint
Yang 2020	Wrong P: AMI or coronary artery in-stent restenosis, Wrong O: platelet reactivity
Yao 2017	Wrong O: outcome only presented as composite endpoint
Zhang 2020	Wrong I/C: prior stroke versus no prior stroke
Zhao 2018	Wrong I and C: dual loading verses no dual loading
Zhu 2015	C missing: everyone was treated with clopidogrel

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Alexopoulos 2015 Greece	RCT Open-label	I: 28 C: 28	0	All-cause mortality n=0 CV mortality n=0	All-cause mortality n=0 CV mortality n=0	STEMI High platelet reactivity High-dose clopidogrel	-	-	-
Angiolillo2016 US	RCT Open-label	I: 49 C: 51	I: 1 C: 2	All-cause mortality n=0 CV mortality n=0	All-cause mortality n=0 CV mortality n=0	Troponin-negative ACS Analysis included drop-outs	-	?	-
Berwanger 2019 Multi-centre	RCT Single-blind (adjudicated endpoints)	I: 1,886 C: 1,913	0	All-cause mortality n=86 (4.6%) CV mortality n=78 (4.1%)	All-cause mortality n=80 (4.2%) CV mortality n=72 (3.8%)	STEMI, post-fibrinolytic therapy, <75 years of age	-	+	-
Cannon 2007 Multi-centre	RCT Double-blind	I: 327 C: 334	0	All-cause mortality n=4 (1.3%) CV mortality n=4 (1.3%)	All-cause mortality n=7 (2.4%) CV mortality n=6 (1.9%)	NSTEMI Patient recruitment 2004-2005	-	+	-
Cao 2019 China	RCT Open-label	I: 48 C: 49	0	All-cause mortality NR CV mortality n=1 (2.1%)	All-cause mortality NR CV mortality n=0	STEMI	-	-	-
Dehghani 2017 Canada	RCT Open-label	I: 68 C: 76	I: 2 C: 2	All-cause mortality n=3	All-cause mortality n=1	STEMI, post-fibrinolytic therapy	?	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Gasecka 2020 Poland	RCT Open-label (for clinical data)	I: 30 C: 30	I: 2 C: 3	All-cause mortality n=0 CV mortality n=0	All-cause mortality n=0 CV mortality n=0	AMI with PCI	-	?	-
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	All-cause mortality n=37 (7%) CV mortality n=18 (4%)	All-cause mortality n=34 (7%) CV mortality n=15 (3%)	NSTE-ACS, ≥70 years	?	+/?	+
Goto 2015 Multi-centre	RCT Double-blind	I: 400 C: 401	I: 63 C: 66	All-cause mortality n=7 (1.8%) CV mortality n=7 (1.8%)	All-cause mortality n=10 (2.5%) CV mortality n=9 (2.2%)	ACS East-Asian countries Analysis included drop-outs	?	+/?	-
Gu 2017 China	RCT Open-label	I: 36 C: 38	0	All-cause mortality NR CV mortality n=0	All-cause mortality NR CV mortality n=0	NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	-	-
Jing 2016 China	RCT Open-label	I: 94 C: 94	0	All-cause mortality n=1	All-cause mortality n=1	STEMI	-	-	-
Li 2015 China	RCT Single-blind	I: 24 C: 24	0	All-cause mortality NR CV mortality n=0	All-cause mortality NR CV mortality n=0	High on-treatment platelet reactivity High-dose clopidogrel	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	All-cause mortality NR CV mortality n=8/281 (2.8%)	All-cause mortality NR CV mortality n=3/161 (1.9%)	STEMI Analysis based on patients without switch	-	-	-
Liu 2017 China	RCT Double-blind	I: 87 C: 86	0	All-cause mortality n=1 (1%)	All-cause mortality n=0	STEMI, diabetes	-	?	-
Liu 2019a China	RCT Open-label	I: 40 C: 40	I: 8 C: 5	All-cause mortality n=0 CV mortality n=0	All-cause mortality n=0 CV mortality n=0	High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor	-	-	-
Liu 2019b China	RCT Open-label	I: 100 C: 108	0	All-cause mortality n=2	All-cause mortality n=2	STEMI, diabetes	-	?	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	All-cause mortality NR CV mortality n=1 (0.9%)	All-cause mortality NR CV mortality n=0	ACS	-	?	-
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	I: 474 C: 474	I: 2 C: 3	All-cause mortality NR CV mortality n=4 (0.8%)	All-cause mortality NR CV mortality n=2 (0.4%)	ACS	?	+/?	-
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	I: 400 C: 400	I: 20 C: 31	All-cause mortality: n=10 (2.5%) CV death: n=6 (1.5%)	All-cause mortality: n=16 (4.1%) CV death: n=15 (3.8%)	ACS Analysis included drop-outs	?	+/?	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Park 2019b South Korea	RCT Open-label	I: 60 C: 60	0	<u>All-cause mortality:</u> n=1 <u>CV mortality:</u> n=0	<u>All-cause mortality:</u> n=0 <u>CV mortality:</u> n=0	ACS with PCI	-	?	-
Tang 2016 China	RCT Open-label	I: 210 C: 210	I: 10 C:10	<u>All-cause mortality</u> n=6 <u>CV mortality</u> n=5	<u>All-cause mortality</u> n=4 <u>CV mortality</u> n=3	STEMI	-	?	-
Wallentin 2009 Multi-centre	RCT Double-blind	I: 9,291 C: 9,333	0	<u>All-cause mortality</u> n=506 (5.9%) <u>CV mortality</u> n=442 (5.1%)	<u>All-cause mortality</u> n=399 (4.5%) <u>CV mortality</u> n=353 (4.0%)	ACS PLATO trial Patient recruitment 2006-2008	?	+	+
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	<u>All-cause mortality</u> n=16 (16%) <u>CV mortality</u> n=15 (15%)	<u>All-cause mortality</u> n=9 (9%) <u>CV mortality</u> n=6 (6%)	ACS, ≥65 years of age	-	?	-
Wang 2016b China	RCT Open-label	I: 87 C: 87	0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=4 (4.6%)	<u>All-cause mortality</u> NR <u>CV mortality</u> n=2 (2.3%)	STEMI, dementia, 60-80 years of age	-	-	-
Wang 2019 China	RCT Open-label	I: 148 C: 150	0	<u>All-cause mortality</u> n=7 (4.7%) <u>CV mortality</u> NR	<u>All-cause mortality</u> n=3 (2.0%) <u>CV mortality</u> NR	STEMI	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wu 2018 China	RCT Open-label	I: 120 C: 124	0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=2	<u>All-cause mortality</u> NR <u>CV mortality</u> n=0	ACS	-	?	-
Xiong 2015 China	RCT Open-label	I:112 C:112	0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=0	ACS CYP2C19 homozygote Unclear dosing of clopidogrel	-	-	-
Yang 2018 China	RCT Open-label	I: 60 C: 60	0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=1	<u>All-cause mortality</u> NR <u>CV mortality</u> n=0	AMI	-	-	-
Yang 2020 China	RCT Open-label	I: 100 C: 100	0	<u>All-cause mortality</u> NR <u>CV mortality</u> n=4 (4%)	<u>All-cause mortality</u> NR <u>CV mortality</u> n=0	ACS	-	-	-
Yao 2017 China	RCT Open-label	I: 60 C: 60	0	<u>All-cause mortality</u> n=1 (1.7%)	<u>All-cause mortality</u> n=0	AMI	-	?	-
You 2020 China	RCT Open-label	I: 195 C: 105	0	<u>All-cause mortality</u> n=29 (14.87%) <u>CV mortality</u> n=23 (11.79%)	<u>All-cause mortality</u> n=6 (5.71%) <u>CV mortality</u> n=5 (4.76%)	STEMI, HPR	-	-	-
Yun 2017 South Korea	RCT Open-label	C: 97 I: 97	0	<u>All-cause mortality</u> n=2	<u>All-cause mortality</u> n=0	STEMI	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zhang 2016 China	RCT Open-label	I: 90 C: 91	0	All-cause mortality n=2 (2.2%) CV mortality n=2 (2.2%)	All-cause mortality n=1 (1.6%) CV mortality n=1 (1.6%)	ACS CYP2C19 poor/intermediate metabolizers High-dose clopidogrel for 7 days, then standard dose	-	-	-
nRCT									
Ahn 2020 South Korea	nRCT Cohort	PS-matched: I: 787 C: 787	N/A	All-cause mortality NR CV mortality n=22 (2.8%)	All-cause mortality NR CV mortality n=17 (2.2%) aHR (95% CI): 0.84 (0.44 to 1.62)	AMI with multivessel disease Population extracted from I: 1,438, C:837 patients	?	?	?
Alexopoulos 2016 Greece	nRCT Cohort	I: 959 C: 717	I: 44 C: 31	All-cause mortality n=59 (6.2%) CV mortality NR	All-cause mortality n=22 (3.1 %) aHR (95% CI): 0.65 (0.38 to 1.11) CV mortality NR	ACS 75 individuals excluded due to lack of information on vital status	?	-	-
Blin 2019 France	nRCT Cohort	PS-matched I: 9,224 C: 9,224	N/A	All-cause mortality n=217 (2.4%) CV mortality NR	All-cause mortality n=150 (1.6%) HR (95% CI): 0.73 (0.59 to 0.90) CV mortality NR	Patients with first ACS and alive at discharge and not transferred to a rehabilitation centre. Population extracted from I: 19,796, C: 13,916	?	?	+
Brener 2019 US	nRCT Cohort	I: 774 C: 665	N/A	All-cause mortality n=58 (6.9%) CV mortality n=31	All-cause mortality n=48 (7.9%) aHR: 1.21 (0.84 to 1.82) CV mortality n=31	ACS	?	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
					aHR: 1.18 (0.72 to 1.94)				
Chang 2020 Taiwan	nRCT Cohort	I: 22,385 C: 10,057	N/A	<u>All-cause mortality</u> Incidence: 16.25//100 person-years	<u>All-cause mortality</u> Incidence: 16.62/100 person-years aHR (95% CI): 0.95 (0.86 to 1.05)	AMI PS weighting	?	-	?
Choe 2019 South Korea	nRCT Cohort	PS-matched I: 1,203 C: 1,203	N/A		<u>All-cause mortality</u> aHR (95% CI): 0.61 (0.34 to 0.93) <u>CV mortality</u> aHR (95% CI): 0.56 (0.35 to 0.91)	ACS Population extracted from I: 7,073, C: 1,474	?	-	+
De Filippo 2019 Multi-centre	nRCT Cohort	*eGFR >60* I: 11,803 C: 2,809 *aGFR <60* I: 1,758 C: 540	N/A	<u>All-cause mortality:</u> *eGFR >60:* n=337 (2.9%) *eGFR <60:* n=195 (11.1%)	<u>All-cause mortality:</u> *eGFR >60:* n=48 (1.7%) aHR (95% CI): 0.77 (0.49 to 1.22) *eGFR <60:* n=27 (5%) aHR (95% CI): 0.45 (0.21 to 0.99)	ACS	-	-	-
Edfors 2018 Sweden	nRCT Cohort	*eGFR >60* I: 24,130 C: 9,538 *eGFR 30-60* I: 7,817 C: 1,986 *eGFR<30* I: 1,525 C: 210	N/A	<u>All-cause mortality</u> *eGFR >60:* n=1,120 (4.8%) *eGFR 30-60:* n=1,252 (18%) *eGFR <30:* n=496 (41%)	<u>All-cause mortality</u> *eGFR >60:* n=212 (2.3%) aHR (95% CI): 0.80 (0.66 to 0.97) *eGFR 30-60:* n=162 (8.7%) aHR (95% CI): 0.83 (0.68 to 1.01) *eGFR <30:* n=55 (33%) aHR (95% CI): 1.08 (0.79 to 1.49)	ACS	?	-	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Giordana 2016 Multi-centre	nRCT Cohort	Europe: I: 8,612 C: 464 East Asia: I: 2,132 C: 136	N/A	<u>All-cause mortality</u> *Europe:* 4.4% *East Asia:* 2.9%	<u>All-cause mortality</u> *Europe:* 1.3% *East Asia:* 0%	ACS	?	-	-
Gosling 2017 UK	nRCT Cohort	I: 4,653 C: 4,917	N/A		<u>All-cause mortality</u> aHR (95% CI): 0.82 (0.71 to 0.96) <u>CV mortality</u> NR	ACS	?	-	?
Hansson 2016 Sweden	nRCT Cohort	I: 978 C: 1,266	N/A	<u>All-cause mortality</u> n=26 (2.7%)	<u>All-cause mortality</u> n=21 (1.7%)	ACS with CABG	-	-	+
Kang 2017 South Korea	nRCT Cohort	I: 6,411 C: 1,708	N/A	<u>All-cause mortality</u> NR <u>CV mortality:</u> n=126 (2.0%)	<u>All-cause mortality</u> NR <u>CV mortality:</u> n=11 (0.6%) HR: NR	ACS but not CABG	-	-	-
Kim 2019 South Korea	nRCT Cohort	I: 15,459 C: 4,811	N/A	<u>All-cause mortality</u> *All patients:* n=319 (2.1%)	<u>All-cause mortality:</u> *All patients:* n=51 (1.1%) aOR (95% CI): 0.57 (0.42 to 0.77) *Patients without treatment switch:* aOR (95% CI): 0.59 (0.41 to 0.87)	ACS sIPTW	-	-	?
Krackhardt 2020 Germany	nRCT Cohort	I: 1,549 C: 1,020	N/A	<u>All-cause mortality</u> n=39 (2.8%)	<u>All-cause mortality</u> n=14 (1.6%) P=0.06	ACS	?	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Krishnamurthy 2019 UK	nRCT Cohort	I: 1,648 C: 811	N/A	<u>All-cause mortality</u> n=193 (11.7%)	<u>All-cause mortality</u> n=77 (9.5%) OR (95%): 0.84 (0.55-1.29)	STEMI	?	-	-
Lee 2018 Taiwan	nRCT Cohort	PS-matched I: 19,112 C: 2,389	N/A	<u>All-cause mortality</u> n=1322 (6.9%)	<u>All-cause mortality</u> n=53 (2.2%) aHR (95% CI): 0.407 (0.308 to 0.536)	AMI who survived more than 30 days after the event Population extracted from I: 24,495, C: 2,844	-	-	+
Ohman 2017 Multi-centre	nRCT (RCT: rivaroxaban versus aspirin)	I: 666 C: 852	N/A	<u>All-cause mortality</u> n=13 (2%) <u>CV mortality</u> n=10 (1.5%)	<u>All-cause mortality</u> n=10 (1.2%) <u>CV mortality</u> n=7 (0.8%)	ACS	+	-	+
Olier 2018 UK	nRCT Cohort	I: 58,248 C: 13,105	N/A	<u>All-cause mortality</u> n=5,656	<u>All-cause mortality</u> n=1,075 aOR (95% CI): 1.058 (0.962 to 1.163)	STEMI	?	-	-
Orenes-Pinero 2019 Spain	nRCT Cohort	I: NR C: NR I & C: 1,717	N/A	<u>All-cause mortality</u> aHR (95% CI): 2.61 (1.16 to 5.90)		ACS, without switching of medication during hospitalisation	?	-	-
Park 2016 South Korea	nRCT Cohort	PS-matched I: 1,377 C: 1,377	Lost to follow-up at 6 months: I: 249 C: 549	<u>All-cause mortality</u> n=36/1,128 (3.2%) <u>CV mortality</u> n=22/1,128 (2.0%)	<u>All-cause mortality</u> n=25/828 (3.0%) OR (95% CI): 0.915 (0.32 to 1.575) <u>CV mortality</u> n=17/828 (2.1%) OR (95% CI): 0.960 (0.482 to 1.913)	AMI Excluded patients who switched during hospitalisation Population extracted from I: 6,633, C: 1,377	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Peyracchia 2020 Multi-centre	nRCT Cohort	PS-matched I: 1,831 C: 798	N/A	<u>All-cause mortality</u> 6.2%	<u>All-cause mortality</u> 2.6% HR: 0.418, P<0.001	ACS with PCI Population extracted from I: 14,105, C:3,356 patients	?	?	-
Rasia 2017 Italy	nRCT Cohort	I: 135 (Plavix), 1,321 (clopidogrel C: 599	N/A	<u>All-cause mortality</u> Plavix: 11.9% Clopidogrel: 5.5%	<u>All-cause mortality</u> 1.7%	ACS Patients with a medication possession ratio <80 excluded	?	-	-
Sahlen 2016 Sweden	nRCT Cohort	I: 33,119 C: 11,954	N/A	<u>All-cause mortality</u> n=4,272 (12.9%)	<u>All-cause mortality</u> n=693 (5.8%) aHR (95% CI): 0.83 (0.75 to 0.92)	AMI	?	-	?
Schmucker 2019 Germany	nRCT Cohort	PS-matched I: 238 C: 238	N/A	<u>All-cause mortality</u>	<u>All-cause mortality</u> HR (95% CI): 0.89 (0.67 to 1.28)	STEMI, ≥75 years Population extracted from I: 552, C: 535 patients	-	-	-
Sheik Rezai 2017 Austria	nRCT Cohort	I: 18,640 C: 7,507	N/A		<u>All-cause mortality</u> aHR (95%CI): 0.7 (0.6 - 0.8)	ACS	-	-	-
Sim 2018 South Korea	nRCT Cohort	PS-matched I: 1,553 C: 1,533	N/A	<u>All-cause mortality</u> n=55 (3.5%)	<u>All-cause mortality</u> n=48 (3.1%) aHR (95% CI): 0.85 (0.57 to 1.26)	Extracted from a Korean AMI register with 13,104 patients	-	?	-
Sim 2019 South Korea	nRCT Cohort	I: 3,180 C: 659	N/A	<u>All-cause mortality</u> n=165 (5.2%)	<u>All-cause mortality</u> n=18 (2.7%)	NSTEMI	-	-	?
Sun 2019 China	nRCT Cohort	PS-matched I: 1,833 C: 1,833	N/A	<u>All-cause mortality:</u> n=52 (2.8%) <u>CV mortality:</u> n=46 (2.5%)	<u>All-cause mortality:</u> n=44 (2.4%) HR: 0.84 (0.56 to 1.26) <u>CV mortality:</u> n=28 (1.5%) HR (95% CI): 0.61 (0.38 to 0.97)	ACS with PCI Population extracted from I: 2,435, C: 2,030 patients	-	?	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Szummer 2020 Sweden	nRCT Cohort	*≥80 years* I: 8,434 C: 5,571 *<80 years* I: 22,415 C: 36,256	N/A	<u>All-cause mortality</u> *≥80 years* Incidence: 18.1/100 person-years) *<80 years* 788 (3.6/100 person-years)	<u>All-cause mortality</u> *≥80 years* Incidence: 10.8/100 person-years HR (95% CI): 1.17 (1.03 to 1.32) *<80 years* Incidence: 1.97/100 person-years HR (95% CI): 0.85 (0.76 to 0.96)	AMI IPTW	+	?	+
Turgeon 2020 Canada	nRCT Cohort	PS-matched I: 3,711 C: 3,711	N/A	<u>All-cause mortality</u> n=54 (1.5%)	<u>All-cause mortality</u> n=61 (1.6%) HR (95% CI): 1.10 (0.75 to 1.61)	ACS with PCI Population extracted from I: 7,109, C: 4,076 patients	?	+	+
Wang 2018 China	nRCT Cohort	PS-matched I: 1,559 C: 779	N/A	<u>All-cause mortality</u> n=19 (1.2%)	<u>All-cause mortality</u> n=7 (0.9%) Chi2 test, P=0.486	ACS Population extracted from I: 20,037, C: 779	-	?	-
Welsh 2019 Multi-centre	nRCT Cohort	I: 6,500 C: 2,188	N/A	<u>All-cause mortality</u> n=298 (4.7%) <u>CV mortality</u> n=249 (3.9%)	<u>All-cause mortality</u> n=45 (2.2%) aHR (95% CI): 0.7 (0.5 to 0.97) <u>CV mortality</u> n=38 (1.9%) aHR (95% CI): 0.7 (0.49 to 1.0)	STEMI	?	-	-
Völz 2020 Sweden	nRCT Cohort	I: 12,168 C: 2,929	N/A	<u>All-cause mortality</u> n=729 (6.1%)	<u>All-cause mortality</u> n=115 (6.3%) aOR (95% CI): 1.28 (0.86 to 1.93)	ACS Instrumental variable 2-stage least squares regression to adjust for confounders	?	?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

*	+	No or minor problems
	?	Some problems
	-	Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	<u>All-cause mortality</u> n=56 HR (95% CI): 1.22 (1.02 to 1.70) <u>CV mortality</u> n=36 HR (95% CI): 1.37 (1.12 to 1.81)	<u>All-cause mortality</u> n=40 <u>CV mortality</u> n=22	Recurrent ACS Unclear clopidogrel dose	-	-	?
Yan 2016 Multi-centre	nRCT Cohort	*With PPI* I: 4,814 C: 351 *Without PPI* I: 4,126 C: 138	N/A	<u>All-cause mortality</u> *With PPI:* n=248 (5.2%) *Without PPI:* n=133 (3.2%)	<u>All-cause mortality</u> *With PPI:* n=9 (2.6%) *Without PPI:* n=1 (0.7%)	ACS Focus: PPI versus no PPI	?	-	-
Yudi 2016 Australia	nRCT Cohort	I: 956 C: 526	N/A	<u>All-cause mortality</u> n=9 (0.9%)	<u>All-cause mortality:</u> n=5 (1.0%)	ACS	?	-	-
Yun 2019 South Korea	nRCT Cohort	PS-matched I: 11,402 C: 11,402	N/A	<u>All-cause mortality</u> 3.9% <u>CV mortality</u> 1.7 % h+	<u>All-cause mortality</u> 3.1% HR (95% CI): 0.76 (0.63 to 0.91) <u>CV mortality</u> 1.0 % HR (95% CI): 0.62 (0.47 to 0.82)	ACS Population extracted from I: 56,216, C: 11,402	?	?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zhao 2020 China	nRCT Cohort	I: 8,520 C: 2,992 *NT-proBNP (ng/L)* *<300* I: 2,874 C: 1,275 *300-1800* I: 3,321 C: 1,130 *>1800* I: 2,325 C: 587	N/A	<u>All-cause mortality</u> *NT-proBNP:* *<300 ng/L* n=10 (0.3%) *300-1800 ng/L* n=22 (0.7%) *>1800 ng/L* n=28 (1.2%) *All NT-proBNP groups:* n=60 (0.7%) <u>CV mortality</u> *All NT-proBNP groups:* n=53 (0.6%)	<u>All-cause mortality</u> *NT-proBNP:* *<300 ng/L* n=4 (0.3%) aHR (95% CI): 1.19 (0.35 to 4.08) *300-1800 ng/L* n=6 (0.5%) aHR (95% CI): 0.78 (0.32 – 1.94) *>1800 ng/L* n=8 (1.4%) aHR (95% CI): 1.42 (0.64 – 3.16) *All NT-proBNP groups:* n=18 (0.6%) aHR NR <u>CV mortality</u> *All NT-proBNP groups:* n=18 (0.6%) aHR NR	STEMI	-	-	-
Zocca 2017 Netherlands	nRCT Historic control	I: 1,009 C: 1,053	N/A	<u>All -cause mortality</u> n=20 (2.0%)	<u>All-cause mortality</u> n=30 (2.9%) HR (95% CI) 1.44 (0.82 to 2.53) PS-matched HR (95% CI): 1.61 (0.88 to 2.95)	ACS	?	-	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.1
Outcome variable: Mortality

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P2: older ACS patients subjected to DAPT									
RCT									
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	All-cause mortality n=37 (7%) CV mortality n=18 (4%)	All-cause mortality n=34 (7%) CV mortality n=15 (3%)	NSTE-ACS, ≥70 years	?	+/?	+
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	All-cause mortality n=16 (16%) CV mortality n=15 (15%)	All-cause mortality n=9 (9%) CV mortality n=6 (6%)	ACS, ≥65 years of age	-	?	-
nRCT									
Schmucker 2019 Germany	nRCT Cohort	PS-matched I: 238 C: 238	N/A	All-cause mortality	All-cause mortality HR (95% CI): 0.89 (0.67 to 1.28)	STEMI, ≥75 years Population extracted from I: 552, C: 535 patients	-	-	-
Szummer 2020 Sweden	nRCT Cohort	I: 8,434 C: 5,571	N/A	All-cause mortality Incidence: 18.1/100 person-years)	All-cause mortality Incidence: 10.8/100 person-years HR (95% CI): 1.17 (1.03 to 1.32)	AMI, ≥80 years IPTW	+	?	+

ACS = acute coronary syndrome, aHR = adjusted hazard ratio aOR = adjusted odds ratio, C = comparison, CI = confidence interval, CV = cardiovascular, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, I = intervention, HPR = high platelet reactivity, HR = hazard ratio, IPTW = inverse probability treatment weighting, N/A = not applicable, NR = not reported, nRCT = non-randomised controlled trial, NSTE-ACS = non-ST-elevation acute coronary syndrome, NSTEMI = non-ST-elevation myocardial infarction, OR = odds ratio, PCI: percutaneous coronary intervention, PS = propensity score, RCT = randomised controlled trial, sIPTW: stabilized inverse probability of treatment weighting SPECT = single-photon emission computed tomography, STEMI = ST-elevation myocardial infarction, UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Alexopoulos 2015 Greece	RCT Open-label	I: 28 C: 28	0	n=0	n=0	STEMI High platelet reactivity High-dose clopidogrel	-	-	-
Berwanger 2019 Multi-centre	RCT Single-blind (adjudicated endpoints)	I: 1,886 C: 1,913	0	n=49 (2.6%)	n=48 (2.5 %)	STEMI, post-fibrinolytic therapy, <75 years of age	-	+	-
Cannon 2007 Multi-centre	RCT Double-blind	I: 327 C: 334	0	n=15 (5.6%)	n=12 (3.8%)	NSTEMI Patient recruitment 2004-2005	-	+	-
Cao 2019 China	RCT Open-label	I: 48 C: 49	0	n=2 (4.2%)	n=1 (2.0%)	STEMI	-	-	-
Dehghani 2017 Canada	RCT Open-label	I: 68 C: 76	I: 2 C: 2	n=1	n=0	STEMI, post-fibrinolytic therapy	?	?	-
Gasecka 2020 Poland	RCT Open-label (for clinical data)	I: 30 C: 30	I: 2 C: 3	n=0	n=0	AMI with PCI	-	?	-
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	n=37 (8%)	n=37 (8)	NSTE-ACS, ≥70 years	?	+/?	+
Goto 2015 Multi-centre	RCT Double-blind	I: 400 C: 401	I: 63 C: 66	n=15 (3.8%)	n=24 (6.0%)	ACS East-Asian countries Analysis included drop-outs	?	+/?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Gu 2017 China	RCT Open-label	I: 36 C: 38	0	n=1 (2.7%)	n=0	NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	-	-
Li 2015 China	RCT Single-blind	I: 24 C: 24	0	n=0	n=0	High on-treatment platelet reactivity High-dose clopidogrel	-	-	-
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	n=6/281 (2.1%)	n=0/161	STEMI Analysis based on patients without switch	-	-	-
Liu 2017 China	RCT Double-blind	I: 87 C: 86	0	n=1 (1%)	n=0	STEMI, diabetes	-	?	-
Liu 2019a China	RCT Open-label	I: 40 C: 40	I: 8 C: 5	n=0	n=0	High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor	-	-	-
Liu 2019b China	RCT Open-label	I: 100 C: 108	0	n=1 (1%)	n=1 (0.9%)	STEMI, diabetes	-	?	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	n=2 (1.8%)	n=1 (1.1%)	ACS	-	?	-
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	I: 474 C: 474	I: 2 C: 3	n=5 (1%)	n=2 (0.4%)	ACS	?	+/?	-
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	I: 400 C: 400	I: 20 C: 31	n=16 (4.0%)	n=20 (5.1%)	ACS Analysis included drop-outs	?	+/?	?
Tang 2016 China	RCT Open-label	I: 210 C: 210	I: 10 C: 10	n=3 (1.5%)	n=0	STEMI	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wallentin 2009 Multi-centre	RCT Double-blind	I: 9,291 C: 9,333	0	n=593 (6.9%)	n=504 (5.8%)	ACS PLATO trial Patient recruitment 2006-2008	?	+	+
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	n=15 (15%)	n= 6 (6%)	ACS, ≥65 years of age	-	?	-
Wang 2016b China	RCT Open-label	I: 87 C: 87	0	n=5 (5.75%)	n=1 (1.15%)	STEMI, dementia, 60-80 years of age	-	-	-
Wang 2019 China	RCT Open-label	I: 148 C: 150	0	n=10 (6.76%)	n=4 (2.67%)	STEMI	-	?	-
Wu 2018 China	RCT Open-label	I: 120 C: 124	0	n=3 (2.5%)	n=0	ACS	-	?	-
Xiong 2015 China	RCT Open label	I: 112 C: 112	0	n=0	n=0	ACS CYP2C19 homozygote Unclear dosing of clopidogrel	-	-	-
Yang 2018 China	RCT Open-label	I: 60 C: 60	0	n=2 (3.3%)	n=1 (1.6%)	AMI	-	-	-
Yao 2017 China	RCT Open-label	I: 60 C: 60	0	n=6 (10%)	n=3 (5%)	AMI	-	?	-
You 2020 China	RCT Open-label	I: 195 C: 105	0	n=11 (5.64%)	n=2 (1.90%)	STEMI, HPR	-	-	-
Zhang 2016 China	RCT Open-label	I: 90 C: 91	0	n=11 (12.2%)	n=3 (3.3%)	ACS CYP2C19 poor/intermediate metabolizers High-dose clopidogrel for 7 days, then standard dose	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
nRCT									
Ahn 2020 South Korea	nRCT Cohort	PS-matched: I: 787 C: 787	N/A	n=23 (2.9%)	n=20 (2.5%) aHR (95% CI): 0.86 (0.47 to 1.58)	AMI with multivessel disease Population extracted from I: 1,438, C:837 patients	?	?	?
Alexopoulos 2016 Greece	nRCT Cohort	I: 959 C: 717	I: 44 C: 31	n=17 (1.8%)	n=8 (1.1%)	ACS 75 individuals excluded due to lack of information on vital status	?	-	-
Brener 2019 USA	nRCT Cohort	I: 774 C: 665	N/A	n=8 (1%)	n=3 (0.45%)	ACS	?	-	-
Chang 2020 Taiwan	nRCT Cohort	I: 22,385 C: 10,057	N/A	Incidence: 5.60/100 person-years	Incidence: 5.79/100 person-years aHR (95% CI): 1.01 (0.85 to 1.19)	AMI PS weighting	?	-	?
Choe 2019 South Korea	nRCT Cohort	PS-matched I: 1,203 C: 1,203	N/A	n=36 (3.0%)	n=28 (2.3%) aHR (95% CI): 0.70 (0.34 to 1.43)	ACS Population extracted from I: 7,073, C: 1,474	?	-	+
De Filippo 2019 Multi-centre	nRCT Cohort	eGFR >60 I: 11,803 C: 2,809 eGFR <60 I: 1,758 C: 540	N/A	*eGFR >60*: 3.8% *eGFR <60:* 7%	*eGFR >60:*2.3% HR (95% CI): NR *eGFR <60:* 3.5% aHR (95% CI): 0.36 (0.16 – 0.81)	ACS	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Edfors 2018 Sweden	nRCT Cohort	eGFR >60 I: 24,130 C: 9,538 eGFR 30-60 I: 7,817 C: 1,986 eGFR<30 I: 1,525 C: 210	N/A	*eGFR >60*: n=1,320 (5.9%) *eGFR 30-60:* n=948 (14%) *eGFR <30:* n=257 (20%)	*eGFR >60:* 244/9535 (3.8%) aHR (95%): 0.93 (0.77 to 1.12) *eGFR 30-60:* n=85 (6.6%) aHR (95%): 0.76 (0.58 to 0.99) *eGFR <30:* n=15 (11%) aHR (95%): 0.62 (0.35 to 1.12)	ACS	?	-	+
Gajanana 2018 US	nRCT Cohort	I: 1,722 C: 861	N/A	n=1 (0.1%)	n=0 (0%)	ACS	?	-	-
Giordana 2016 Multi-centre	nRCT Cohort	European I: 8,612 C: 464 Asian I: 2,132 C: 136	NA	European: 4.1% Asian: 1.4%	European: 3.0% Asian: 0%	ACS	?	-	-
Grimaldi-Bensouda 2018 France	nRCT Case-control	1,047 cases with recurrent MI 2,234 matched controls without recurrent MI	N/A		aOR (95% CI): 0.65 (0.52 to 0.81)	MI	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Kang 2017 South Korea	nRCT Cohort	I: 6,411 C: 1,708	N/A	n=102 (1.6%)	n=20 (1.2%)	ACS but not CABG No results regarding MI in the PS-matched cohort	-	-	-
Kim 2017 US	nRCT Cohort	PS-matched I: 9,505 C: 2,376	N/A	1.91%	1.40%	ACS, private insurance register Population extracted from I: 22,168, C: 2,524	?	-	-
Kim 2019 South Korea	nRCT Cohort	I: 15,459 C: 4,811	N/A	n=1,245 (8.1 %)	n=423 (8.8%) aOR (95%): 1.15 (1.02 to 1.29)	ACS sIPTW	-	-	?
Krackhardt 2020 Germany	nRCT Cohort	I: 1,549 C: 1,020	N/A	n=25 (1.8%)	n=22 (2.5%) P=0.257	ACS	?	-	-
Krishnamurthy 2019 UK	nRCT Cohort	I: 1,648 C: 811	N/A	n=108 (6.6%)	n=26 (3.2%) aOR (95% CI): 0.54 (0.32 to 0.93)	STEMI	?	-	-
Lee 2018 Taiwan	nRCT Cohort	PS-matched I: 19,112 C: 2,389	N/A	n=1,726 (9%)	n= 180 (7.5%) aHR (95% CI): 0.984 (0.807 to 1.199)	AMI who survived more than 30 days after the event Population extracted from I: 24,495, C: 2,844	-	-	+
Ohman 2017 Multi-centre	nRCT (RCT: rivaroxaban versus aspirin)	I: 666 C: 852	N/A	n=26 (3.9%)	n=23 (2.7%)	ACS	+	-	?
Park 2016 South Korea	nRCT Cohort	PS-matched I: 1,377 C: 1,377	Lost to follow-up at 6 months: I: 249 C: 549	n=15/1,128 (1.3%)	n=10/828 (1.2%) aHR: 0.851 (0.381 to 1.899)	AMI Excluded patients who switched during hospitalisation Population extracted from I: 6,633, C: 1,377	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Peyracchia 2020 Multi-centre	nRCT Cohort	PS-matched I: 1,831 C: 798	N/A	3.3%	0.4% HR (95% CI): 0.112, P<0.001	ACS with PCI Population extracted from I: 14,105, C:3,356 patients	?	?	-
Rasia 2017 Italy	nRCT Cohort	I: 135 (Plavix), 1,321 (clopidogrel C: 599	N/A	Plavix: 6.7% Clopidogrel: 5.4%	4.3%	ACS Patients with a medication possession ratio <80 excluded	?	-	-
Sahlen 2016 Sweden	nRCT Cohort	I: 33,119 C: 11,954	N/A	10.8%	6.1% aHR (95% CI): 0.89 (0.78 to 1.01)	AMI	?	-	?
Schmucker 2019 Germany	nRCT Cohort	I: 552 C: 535	N/A	Reinfarction 4.8%	Reinfarction 3.5%	STEMI , ≥75 No PS-matched results provided regarding MI	-	-	-
Sim 2018 South Korea	nRCT Cohort	PS-matched I: 1,553 C: 1,553	N/A	n=24 (1.5%)	n=27 (1.7%) aHR (95% CI): 1.09 (0.61 to 1.95)	Extracted from a Korean AMI register with 13,104 patients	-	?	-
Sim 2019 South Korea	nRCT Cohort	I: 3,180 C: 659	N/A	n=64 (2%)	n=11 (1.7%)	NSTEMI	-	-	?
Sun 2019 China	nRCT Cohort	PS-matched I: 1,833 C: 1,833	N/A	n=11 (0.6%)	n=15 (0.8%) HR (95% CI): 1.36 (0.63 to 2.96)	ACS with PCI Population extracted from I: 2,435, C: 2,030 patients	-	?	?
Szummer 2020 Sweden	nRCT Cohort	*≥80 years* I: 8,434 C: 5,571 *<80 years* I: 22,415 C: 36,256	N/A	*≥80 years* Incidence: 13.9/100 person-years *<80 years* Incidence: 4.7/100 person-years	*Age ≥80 years* Incidence: 7.5/100 person-years aHR: 0.80 (0.70 to 0.92) *Age <80 years* Incidence: 3.0/100 person-years aHR: 0.82 (0.75 to 0.91)	AMI IPTW	+	?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Turgeon 2020 Canada	nRCT Cohort	PS-matched I: 3,711 C: 3,711	N/A	ACS n=228 (6.1%)	ACS n=235 (6.3%) HR (95% CI): 1.02 (0.75 to 1.61)	ACS with PCI Population extracted from I: 7,109, C: 4,076 patients	?	+	+
Wang 2018 China	nRCT Cohort	PS-matched I: 1,559 C: 779	N/A	n=15 (1%)	n=5 (0.6%) P=0.427	ACS Population extracted from I: 20,037, C: 779	-	?	-
Welsh 2019 Multi-centre	nRCT Cohort	I: 6,500 C: 2,188	N/A	n=160 (2.5%)	n=34 (1.7%)	STEMI	?	-	-
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	n=32 (5.7%) HR (95% CI): 1.171 (0.556 to 1.409)	n=28 (5.3%)	Recurrent ACS Unclear clopidogrel dose	-	?	-
Yan 2016 Multi-centre	nRCT Cohort	With PPI: I: 4,814 C: 351 Without PPI: I: 4,126 C: 138	N/A	With PPI: n=213 (4.3%) Without PPI: n=186 (4.5%)	With PPI: n=2 (0.6%) Without PPI: n=0 (0%)	ACS Focus: PPI versus no PPI	?	-	-
Yudi 2016 Australia	nRCT Cohort	I: 956 C: 526	N/A	n=17 (1.8%)	n=11 (2.1%)	ACS	?	-	-
Yun 2019 South Korea	nRCT Cohort	PS-matched I: 11,402 C: 11,402	N/A	10.0 %	10.6 % HR (95% CI): 1.07 (0.97 to 1.18)	ACS Population extracted from I: 56,216, C: 11,402	?	?	+
Zhao 2020 China	nRCT Cohort	I: 8,520 C: 2,992	N/A	n=19 (0.2%)	n=3 (0.1%) P=0.186	STEMI	-	-	-
Zocca 2017 Netherlands	nRCT Historical control	I: 1,009 C: 1,053	N/A	n=24 (2.4%)	n=29 (2.8%) aHR (95% CI): 1.39 (0.78 to 2.48)	ACS	?	-	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.2
Outcome variable: Myocardial infarction

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P2: older ACS patients subjected to DAPT									
RCT									
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	n=37 (8%)	n=37 (8)	NSTE-ACS, ≥70 years	?	+/?	+
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	n=15 (15%)	n= 6 (6%)	ACS, ≥65 years of age	-	?	-
nRCT									
Schmucker 2019 Germany	nRCT Cohort	I: 552 C: 535	N/A	Reinfarction 4.8%	Reinfarction 3.5%	STEMI , ≥75 No PS-matched results provided regarding MI	-	-	-
Szummer 2020 Sweden	nRCT Cohort	I: 8,434 C: 5,571	N/A	Incidence: 13.9/100 person-years	Incidence: 7.5/100 person-years aHR: 0.80 (0.70 to 0.92)	AMI, ≥80 years IPTW	+	?	+

ACS = acute coronary syndrome, aHR = adjusted hazard ratio aOR = adjusted odds ratio, C = comparison, CI = confidence interval, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, I = intervention, HR = hazard ratio, N/A = not applicable, nRCT = non-randomised controlled trial, NSTEMI = non-ST-elevation myocardial infarction, OR = odds ratio, PS = propensity score, RCT = randomised controlled trial, sIPTW: stabilized inverse probability of treatment weighting, STEMI = ST-elevation myocardial infarction, UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Alexopoulos 2015 Greece	RCT Open-label	I: 28 C: 28	0	Clinically significant bleeding (BARC) n=1 (3.5%) Major bleeding NR All bleedings NR	Clinically significant bleeding (BARC) n=2 (7%) Major bleeding NR All bleedings NR	STEMI High platelet reactivity High-dose clopidogrel	-	-	-
Angiolillo 2016 US	RCT Open-label	I: 49 C: 51	I: 1 C: 2	Clinically significant bleeding NR Major bleeding NR All bleedings n=0 Minor bleedings (CURE) n=0	Clinically significant bleeding NR Major bleeding NR All bleedings n=4 Minor bleedings (CURE) n=2 (7.8%)	Troponin-negative ACS Bleedings only included if assessed as drug-related, unclear assessment	-	?	-
Berwanger 2019 Multi-centre	RCT Single-blind (adjudicated endpoints)	I: 1,886 C: 1,913	0	Clinically significant bleeding (TIMI) n=71 (3.8%) Major bleeding (TIMI) n=23 (1.2%) All bleedings n=116 (6.2%)	Clinically significant bleeding (TIMI) n=101 (5.3%) Major bleeding (TIMI) n=20 (1.0%) All bleedings n=196 (10.2%)	STEMI, post-fibrinolytic therapy, <75 years of age	-	+	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Cannon 2007 Multi-centre	RCT Double-blind	I: 327 C: 334	0	Clinically significant bleeding NR1 Major bleeding (TIMI) n=26 (8.7%) All bleedings n=30 (9.9%)	Clinically significant bleeding NR Major bleeding (TIMI) n=26 (8.6%) All bleedings n= 34 (10.5%)	NSTEMI Patient recruitment 2004 -2005	-	+	-
Cao 2019 China	RCT Open-label	I: 48 C: 49	0	Clinically significant bleeding NR Major bleeding NR All bleedings n=1 (2.1%)	Clinically significant bleeding NR Major bleeding NR All bleedings n=2 (4.1%)	STEMI Bleedings not defined	-	-	-
Dehghani 2017 Canada	RCT Open-label	I: 68 C: 76	I: 2 C: 2	Clinically significant bleeding NR Major bleeding (BARC) n=1 (1.4%) All bleedings NR	Clinically significant bleeding NR Major bleeding (BARC) n=2 (2.6%) All bleedings NR	STEMI, post-fibrinolytic therapy	?	?	-
Gasecka 2020 Poland	RCT Open-label (fo clinical data)	I: 30 C: 30	I: 2 C: 3	Clinically significant bleeding NR Major bleeding (not defined) n=1 All bleedings NR	Clinically significant bleeding NR Major bleeding (not defined) n=1 All bleedings NR	AMI with PCI	-	-?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	Clinically significant bleeding (PLATO) n=88 (18%) Major bleeding (TIMI) n=9 (2%) All bleedings NR	Clinically significant bleeding (PLATO) n=118 (24%) Major bleeding (TIMI) n=21 (4%) All bleedings NR	NSTE-ACS, ≥70 years	?	+/?	+
Goto 2015 Multi-centre	RCT Double-blind	I: 380 C: 387 (safety population)	0	Clinically significant bleeding (PLATO) n=56 (14.7%) Major bleeding (PLATO) n=26 (6.8%) All bleedings NR	Clinically significant bleeding (PLATO) n=92 (23.8%) Major bleeding (PLATO) n=40 (10.3%) All bleedings NR	ACS East-Asian countries	?	+/?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Gu 2017 China	RCT Open-label	I: 36 C: 38	0	Clinically significant bleeding NR Major bleeding (TIMI) n=0 All bleedings NR	Clinically significant bleeding NR Major bleeding (TIMI) n=0 All bleedings NR	NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	-	-
Jing 2016 China	RCT Open-label	I: 94 C: 94	0	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=17 (18%)	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=23 (24%)	STEMI	-	-	-
Li, 2015 China	RCT Single-blind	I: 24 C: 24	0	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=4 (17%)	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=3 (13%)	High on-treatment platelet reactivity High-dose clopidogrel	-	-	-
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	Clinically significant bleeding (BARC) n=10/281 (3.6%) Major bleeding NR All bleedings n=34 (12.1%)	Clinically significant bleeding (BARC) n=3/161 (1.9%) Major bleeding NR All bleedings n=31 (19.3%)	STEMI Analysis based on patients without switch	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Liu 2017 China	RCT Double-blind	I: 87 C: 86	0	Clinically significant bleeding NR Major bleeding (Severe bleeding, not defined) n=0 All bleedings NR	Clinically significant bleeding NR Major bleeding (Severe bleeding, not defined) n=3 (3%) All bleedings NR	STEMI, diabetes	-	?	-
Liu 2019a China	RCT Open-label	I: 40 C: 40	I: 8 C: 5	Clinically significant bleeding NR Major bleeding (own definition) n=0 All bleedings NR	Clinically significant bleeding NR Major bleeding (own definition) n=0 All bleedings NR	High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor	-	-	-
Liu 2019b China	RCT Open-label	I: 100 C: 108	0	Clinically significant bleeding NR Major bleeding (massive bleeding) n=1 All bleedings n=5	Clinically significant bleeding NR Major bleeding (massive bleeding) n=1 All bleedings n=8	STEMI, diabetes GUSTO bleeding classification	-	?	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=1 (0.9%)	Clinically significant bleeding NR Major bleeding n=0 All bleedings n=2 (2.1%)	ACS Bleedings not defined	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	I: 474 C: 474	I: 2 C: 3	Clinically significant bleeding NR Major bleeding n=22 All bleedings NR	Clinically significant bleeding NR Major bleeding n=36 All bleedings NR	ACS Major bleedings not defined	?	+/?	-
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	I: 400 C: 400	I: 20 C: 31	Clinically significant bleeding (BARC) n=24 (6.1%) Major bleeding (TIMI) n=8 (2.0%) All bleedings NR	Clinically significant bleeding (BARC) n=41 (10.6%) Major bleeding (TIMI) n=19 (4.9%) All bleedings NR	ACS Analysis included drop-outs	?	+/?	?
Park 2019b South Korea	RCT Open-label	I: 60 C: 60	0	Clinically significant bleeding NR Major bleeding n=0 All bleedings NR	Clinically significant bleeding NR Major bleeding n=0 All bleedings NR	ACS with PCI Major bleedings not defined	-	?	-
Tang 2016 China	RCT Open-label	I: 210 C: 210	I: 10 C: 10	Clinically significant bleeding NR Major bleeding (TIMI) n=2 All bleedings n=7 (3.5%)	Clinically significant bleeding NR Major bleeding (TIMI) n=0 All bleedings n=10 (5%)	STEMI	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wallentin 2009 Multi-centre	RCT Double-blind	I: 9,186 C: 9,235 (safety population)	0	Clinically significant bleeding (PLATO) n=1,215 (14.6%) Major bleeding (TIMI) n=638 (7.7%) All bleedings NR	Clinically significant bleeding (PLATO) n=1,339 (16.1%) Major bleeding (TIMI) n=657 (7.9%) All bleedings NR	ACS PLATO trial Patient recruitment 2006-2008	?	+	+
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	Clinically significant bleeding NR Major bleeding (PLATO) n=6 (6%) All bleedings n=14 (14%)	Clinically significant bleeding NR Major bleeding (PLATO) n=8 (8%) All bleedings n=21 (21%)	ACS, ≥65 years of age	-	?	-
Wang 2019 China	RCT Open-label	I: 148 C: 150	0	Clinically significant bleeding NR Major bleeding (TIMI) n=4 (2.7%) All bleedings n=16 (10.81%)	Clinically significant bleeding NR Major bleeding (TIMI) n=5 (3.33%) All bleedings n=22 (14.67%)	STEMI	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wu 2018 China	RCT Open-label	I: 120 C: 124	0	Clinically significant bleeding NR Major bleeding NR All bleedings n=4 (3.3%)	Clinically significant bleeding NR Major bleeding NR All bleedings n=14 (11%)	ACS	-	?	-
Xiong 2015 China	RCT Open-label	I: 112 C: 112	0	Clinically significant bleeding NR Major bleeding (not defined) n=0 All bleedings n=23 (20.5%)	Clinically significant bleeding NR Major bleeding (not defined) n=0 All bleedings n=8 (7.1%)	ACS CYP2C19 homozygote Unclear dosing of clopidogrel	-	-	-
Xue 2016 China	RCT Double-blind	I: 25 C: 25	I: 5 C: 4	Clinically significant bleeding NR Major bleeding (PLATO) n=0 All bleedings n=0	Clinically significant bleeding NR Major bleeding (PLATO) n=0 All bleedings n=3 (12%)	NSTEMI	-	-	-
Yang 2018 China	RCT Open-label	I: 60 C: 60	0	Clinically significant bleeding NR Major bleeding (not defined) n=0 All bleedings NR	Clinically significant bleeding NR Major bleeding (not defined) n=0 All bleedings NR	AMI	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Yao 2017 China	RCT Open-label	I: 60 C: 60	0	Clinically significant bleeding n=1 Major bleeding (BARC) n=1 All bleedings NR	Clinically significant bleeding n=0 Major bleeding (BARC) n=0 All bleedings NR	AMI	-	?	-
You 2020 China	RCT Open-label	I: 195 C: 105	0	Clinically significant bleeding NR Major bleeding (TIMI) n=3 (1.54%) All bleedings NR	Clinically significant bleeding NR Major bleeding (BARC) n=5 (4.76%) All bleedings NR	STEMI, HPR	-	-	-
Zhang 2016 China	RCT Open-label	I: 90 C: 91	0	Clinically significant bleeding NR Major bleeding (PLATO) n=2 (2.2%) All bleedings NR	Clinically significant bleeding NR Major bleeding (PLATO) n=1 (1.6%) All bleedings NR	ACS CYP2C19 poor/intermediate metabolizers High-dose clopidogrel for 7 days, then standard dose	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
nRCT									
Ahn 2020 South Korea	nRCT Cohort	PS- matched: I: 787 C: 787	N/A	Clinically significant bleeding NR Major bleeding (TIMI) n=16 (2.0%) All bleedings NR	Clinically significant bleeding NR Major bleeding (TIMI) n=26 (3.3%) aHR (95% CI): 1.69 (0.89 to 3.20) All bleedings NR	AMI with multivessel disease Population extracted from I: 1,438, C:837 patients	?	?	?
Alexopoulos 2016 Greece	nRCT Cohort	I: 959 C: 717	I: 44 C: 31	Clinically significant bleeding (BARC) n=91 (9.5%) Major bleeding (BARC) n=54 (5.6%) All bleedings (BARC, any type) n=361 (37.6%)	Clinically significant bleeding (BARC) n= 87 (12.1%) aHR (95% CI): 1.51 (1.10 to 2.07) Major bleeding (BARC) n=39 (5.4%) aHR (95% CI): 1.35 (0.86 to 2.13) All bleedings (BARC, any type) n=408 (56.9%) aHR (95% CI): 1.81 (1.55 to 2.10)	ACS 75 individuals excluded due to lack of information on vital status Adjusted for age, gender, BMI, number of cardiovascular risk factors	?	-	-
Antoniou 2018 UK	nRCT Cohort	I: 520 C: 1,203	N/A	Clinically significant bleeding (BARC) n= 26 (5.1%) Major bleeding NR All bleedings NR	Clinically significant bleeding (BARC) n=66 (5.5%) P=0.86 Major bleeding NR All bleedings NR	ACS	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Blin 2019 France	nRCT Cohort	PS-matched I: 9,224 C: 9,224	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalization for bleeding) n=170 (1.8%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalization for bleeding) n=163 (1.8%) aHR (95% CI): 1.02 (0.82 to 1.26) <u>All bleedings</u> NR	Patients with first ACS and alive at discharge and not transferred to a rehabilitation centre. Population extracted from I: 19,796, C: 13,916	?	?	+
Brener 2019 US	nRCT Cohort	I: 774 C: 665	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalisation for bleeding) n=4 <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalisation for bleeding) n=1 <u>All bleedings</u> NR	ACS	?	-	-
Chang 2020 Taiwan	nRCT Cohort	I: 22,385 C: 10,057	N/A	<u>Clinically significant bleeding</u> (BARC 2, 3 or 5) Incidence: 18.35/100 person-years <u>Major bleeding</u> (BARC 3 or 5) Incidence: 3.27/100 person-year <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> (BARC 2, 3 or 5) Incidence: 21.59/100 person-years aHR (95% CI): 1.16 (1.06 to 1.27) <u>Major bleeding</u> (BARC 3 or 5) Incidence: 2.92/100 person-years aHR (95% CI): 0.86 (0.68 to 1.09) <u>All bleedings</u> NR	AMI PS weighting	?	-	?
Choe 2019 South Korea	nRCT Cohort	PS-matched I: 1,203 C: 1,203	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (TIMI) n=34 (2.8%)	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (TIMI) n=39 (3.2%)	ACS Bleeding only in hospital before discharge Population extracted from I: 7,073, C: 1,474	?	-	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
				  <u>All bleedings</u> NR	aOR (95% CI): 1.16 (0.86 to 1.86) <u>All bleedings</u> NR				
De Filippo 2019 Multi-centre	nRCT Cohort	eGFR >60 I: 11,803 C: 2,809 eGFR <60 I: 1,758 C: 540	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC) aHR (95%CI): *eGFR>60:* NR *eGFR<60*: 0.87 (0.45 to 1.66) <u>All bleedings</u> NR	ACS	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
\- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Edfors 2018 Sweden	nRCT Cohort	eGFR >60 I: 24,130 C: 9,538 eGFR 30-60 I: 7,817 C: 1,986 eGFR<30 I: 1,525 C: 210	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (Readmission with bleeding) *eGFR >60*: n=732 (3.2%) *eGFR 30-60:* n=397 (5.6%) *eGFR <30:* n=121 (9.1%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (Readmission with bleeding) *eGFR >60:* n=241 (3.7 %) aHR (95% CI): 1.10 (0.90 to 1.35) *eGFR 30-60:* n=94 (7.4%) aHR (95% CI): 1.13 (0.84 to 1.51) *eGFR <30:* n=20 (15%) aHR (95% CI): 1.79 (1.00 to 3.21) <u>All bleedings</u> NR	ACS	?	-	+
Gajanana 2018 US	nRCT Cohort	I: 1,722 C: 861	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> n=44/1721 (3%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> n=7/860 (0.8%) <u>All bleedings</u> NR	ACS In-hospital stay only Major bleeding defined as any gastrointestinal bleeding, hematocrit drop >15, or hematoma (> 4cm) with hematocrit >15	?	-	-
Giordana 2016 Multi-centre	nRCT Cohort	European I: 8,612 C: 464 Asian I: 2,132 C: 136	N/A	<u>Clinically significant</u> NR <u>Major bleeding</u> 2.9% (European), 2.6% (Asian) <u>All bleedings:</u> NR	<u>Clinically significant</u> NR <u>Major bleeding</u> 5% (European), 1.5% (Asian) <u>All bleedings:</u> NR	ACS Major bleeding: Serious bleeding defined as intracranial bleeding or any other bleeding leading to hospitalisation and/or red blood transfusion or in-hospital bleeding defined as TIMI major/ minor or BARC 3	?	-	-
Hansson 2016 Sweden	nRCT Cohort	I: 978 C: 1,266	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC 4: CABG-related)	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC 4: CABG-related)	ACS with CABG	-	-	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
				n=172 (17.6%) All bleedings NR	n=163 (12.9%) aOR (95% CI): 0.72 (0.56 to 0,92) All bleedings NR				
Kang 2017 South Korea	nRCT Cohort	PS-matched I: 572 C: 572	N/A	Clinically significant bleeding (BARC 2, 3 or 5) 3.1% Major bleeding (BARC 3 or 5) n=51/6,411 (1.0%) All bleedings NR	Clinically significant bleeding (BARC 2, 3 or 5) 8% aHR: 2.65 (1.53 to 4.56) Major bleeding (BARC 3 or 5) n=16/1,708 (1.1%) All bleedings NR	ACS but not CABG Population extracted from I: 6,411, C: 1,708	-	-	+
Kim 2019 South Korea	nRCT Cohort	I: 15,459 C: 4,811	N/A	Clinically significant bleeding NR Major bleeding NR All bleedings NR Intracranial, gastrointestinal and other bleedings: n=136 (0.9%)	Clinically significant bleeding NR Major bleeding NR All bleedings NR Intracranial, gastrointestinal and other bleedings: n=44 (0.9%) aOR (95% CI): 1.11 (0.78 to 1.57)	ACS sIPTW	-	-	?
Krackhardt 2020 Germany	nRCT Cohort	I: 1,549 C: 1,020	N/A	Clinically significant bleeding NR Major bleeding (BARC) n=8 (0.6%)	Clinically significant bleeding NR Major bleeding BARC) n=5 (0.6%) P=0.978	ACS	?	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
				<u>All bleedings</u> NR	<u>All bleedings</u> NR				
Krishnamurthy 2019 UK	nRCT Cohort	I: 1,648 C: 811	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (HORIZONS criteria) n=95 (6.1%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (HORIZONS criteria) n=37 (4.6%) aOR (95% CI): 0.98 (0.64 to 1.52) <u>All bleedings</u> NR	STEMI Major bleeding according to HORIZONS criteria: intracranial or intraocular bleeding; access site bleeding of diameter of ≥5 cm, or requiring intervention; a reduction in haemoglobin of ≥40 g/L without an overt source of bleeding, or ≥30 g/L with an overt source of bleeding; re-operation for bleeding and blood transfusion	?	-	-
Lee 2018 Taiwan	nRCT Cohort	PS-matched I: 19,112 C: 2,389	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> n=779 (4.1%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> n=76 (3.2%) aHR (95% CI): 0.731 (0.542 to 1.026) <u>All bleedings</u> NR	AMI who survived more than 30 days after the event Major bleeding defined as major GI bleeding and/or intracerebral hemorrhage Population extracted from I: 24,495, C: 2,844	-	-	+
Ohman 2017 Multi-centre	nRCT (RCT: rivaroxaban versus aspirin)	I: 666 C: 852	N/A	<u>Clinically significant bleeding</u> (TIMI, non-CABG) n=23 (3.5%) <u>Major bleeding</u> (TIMI) n=0	<u>Clinically significant bleeding</u> (TIMI non-CABG) n=51 (6.0%) <u>Major bleeding</u> (TIMI) n=8 (0.9%)	ACS	+	-	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
				<u>All bleedings</u> NR	<u>All bleedings</u> NR				
Olier 2018 UK	nRCT Cohort	I: 58,248 C: 13,105	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (in-hospital, own definition) n=843 <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (in-hospital, own definition) n=76 aOR (95% CI): 0.648 (0.493 to 0.852) <u>All bleedings</u> NR	STEMI Major bleeding in hospital: GI, IC, retroperitoneal hematoma, tamponade, transfusion, punction site complication leading to intervention	?	-	-
Park 2016 South Korea	nRCT Cohort	PS-matched C: 1,377 I: 1,377	Lost to follow-up at 6 months: I: 249 C: 549	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (TIMI) n=17 (1.2%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (TIMI) n=36 (2.6%) OR (95% CI): 1.971 (1.086-3.577) <u>All bleedings</u> NR	AMI Excluded patients who switched during hospitalisation Population extracted from I: 6,633, C: 1,377	-	-	-
Peyracchia 2020 Multi-centre	nRCT Cohort	PS-matched I: 1,831 C: 798	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC) 3.3% <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (BARC) 4.3% P=0.212 <u>All bleedings</u> NR	ACS with PCI Population extracted from I: 14,105, C:3,356 patients	?	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Rasia 2017 Italy	nRCT Cohort	I: 135 (Plavix), 1,321 (clopidogrel) C: 599	N/A	<u>Clinically significant</u> (own definition) Plavix: 3.7% Clopidogrel: 1.4% <u>Major bleeding</u> NR <u>All bleedings</u> NR	<u>Clinically significant</u> (own definition) 0.7% <u>Major bleeding</u> NR <u>All bleedings</u> NR	ACS Patients with a medication possession ratio <80 excluded Clinically significant bleeding: in publication called "major bleeding" and defined as clinically significant, requiring medical observation and hospitalisation and/or treatment by a health care professional	?	-	-
Sahlen 2016 Sweden	nRCT Cohort	I: 33,119 C: 11,954	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (bleeding requiring admission) 5.2% <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (bleeding requiring admission) 5.5% aHR (95% CI): 1.2 (1.04 to 1.4) <u>All bleedings</u> NR	AMI	?	-	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Schmucker 2019 Germany	nRCT Cohort	PS-matched I: 238 C: 238	N/A	Clinically significant bleeding Major bleeding NR All bleedings NR	Clinically significant bleeding HR (95% CI): 1.08 (0.49 to 2.37) Major bleeding NR All bleedings NR	STEMI, ≥75 years Population extracted from I: 552, C: 535 patients Clinically significant bleeding included in-hospital bleedings (TIMI major, minor, minimal) and serious bleedings requiring medical attention after discharge	-	-	-
Sim 2018 South Korea	nRCT Cohort	PS- matched I: 1,553 C: 1,553	N/A	Clinically significant bleeding NR Major bleeding (TIMI) n=22 (1.4%) All bleedings NR	Clinically significant bleeding NR Major bleeding (TIMI) n=44 (2.8%) aHR (95% CI): 2.05 (1.22 to 3.45) All bleedings NR	Extracted from a Korean AMI register with 13,104 patients	-	?	+
Sim 2019 South Korea	nRCT	I: 3,180 C: 659	N/A	Clinically significant bleeding NR Major bleeding (TIMI) n=45 (1.4%) All bleedings NR	Clinically significant bleeding NR Major bleeding (TIMI) n=17 (2.6%) All bleedings NR	NSTEMI	-	-	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
\- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Spoendlin 2018 US	nRCT Cohort	PS-matched I: 3,013 C: 3,013	N/A	Clinically significant bleeding NR Major bleeding (inpatient bleeding) n=44 All bleedings NR	Clinically significant bleeding NR Major bleeding (inpatient bleeding) n=30 HR (95% CI): 0.80 (0.51 to 1.27) All bleedings NR	ACS and diabetes Population extracted from I: 24,079, C: 3,044	-	+	?
Sun 2019 China	nRCT Cohort	PS-matched I: 1,833 C: 1,833	N/A	Clinically significant bleeding NR Major bleeding (BARC) n=27 (1.5%) All bleedings NR	Clinically significant bleeding NR Major bleeding (BARC) n=39 (2.1%) HR (95% CI): 1.45 (0.89 to 2.39) All bleedings NR	ACS with PCI Population extracted from I: 2,435, C: 2,030 patients	-	?	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Szummer 2020 Sweden	nRCT Cohort	*≥80 years* I: 8,434 C: 5,571 *<80 years* I: 22,415 C: 36,256	N/A	<u>Clinically significant</u> NR <u>Major bleeding</u> (readmission for bleeding) *≥80 years* Incidence: 4.86/100 person-years) *<80 years* Incidence: 2.82/100 person-years) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (readmission for bleeding) *≥80 years* Incidence: 6.90/100 person-years aHR (95% CI): 1.48 (1.25 to 1.76) *<80 years* Incidence: 3.32/100 person-years aHR (95% CI): 1.32 (1.18 to 1.47) <u>All bleedings</u> NR	AMI IPTW	+	?	+
Turgeon 2020 Canada	nRCT Cohort	PS-matched I: 3,711 C: 3,711	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalisation) n=182 (4.9%) <u>All bleedings</u> NR	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> (hospitalisation) n=261 (7.0%) aHR (95% CI): 1.52 (1.24 to 1.87) <u>All bleedings</u> NR	ACS with PCI Population extracted from I: 7,109, C: 4,076 patients	?	+	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wang 2018 China	nRCT Cohort	PS-matched I: 1,558 C: 779	N/A	Clinically significant bleeding (BARC) n=6 (0.4%) Major bleeding (BARC) n=3 (0.2%) All bleedings n=16 (1%)	Clinically significant bleeding (BARC) n=8 (1%) Major bleeding (BARC) n=6 (0.8%) All bleedings n=18 (2.3%)	ACS Population extracted from I: 20,037, C: 779	-	?	-
Welsh 2019 Multi-centre	nRCT Cohort	I: 6,500 C: 2,188	N/A	Clinically significant bleeding NR Major bleeding n=114 (1.8%) All bleedings NR	Clinically significant bleeding NR Major bleeding n=23 (1.1%) aHR (95% CI): 0.47 (0.29 to 0.76) All bleedings NR	STEMI Major bleeding: severe (fatal, leading to a decrease in hemoglobin>5g/dl, significant hypotension, requiring surgery, symptomatic intracranial hemorrhage, requiring transfusion of 4 or more units) and other non-severe (significantly disabling, intraocular bleeding leading to vision loss, or requiring transfusion of 2-3 units)	?	-	-
Vyas 2017 US	nRCT Cohort	I: 7,283 C: 1,049	N/A	Clinically significant bleeding NR Major/life threatening bleeding 7.9% All bleedings NR	Clinically significant bleeding NR Major/life threatening bleeding 6.9% All bleedings NR	ACS Population based on insurance membership	-	-	-
Völz 2020 Sweden	nRCT Cohort	I: 12,168 C: 2,929	N/A	Clinically significant bleeding (BARC 2 or 3) n=489 (4.2%) Major bleeding	Clinically significant bleeding (BARC 2 or 3) n=163 (6.6%) aOR (95% CI): 2.88 (1.53 to 5.44) Major bleeding	ACS Instrumental variable 2-stage least squares regression to adjust for confounders	?	?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
				NR All bleedings NR	NR All bleedings NR				
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	Clinically significant bleeding NR Major bleeding (TIMI) n=42 Reported crude HR (95% CI): 1.23 (0.59 to 1.90) All bleedings NR	Clinically significant bleeding NR Major bleeding (TIMI) n=45 All bleedings NR	Recurrent ACS Unclear clopidogrel dose	-	-	-
Yan 2016 Multi-centre	nRCT Cohort	With PPI: I: 4,814 C: 351 Without PPI: I: 4,126 C: 138	N/A	Clinically significant bleeding NR Major bleeding (Severe bleeding) With PPI: n=181 (3.8%) Without PPI: n=111 (2.7%) All bleedings NR	Clinically significant bleeding NR Major bleeding (Severe bleeding) With PPI: n=17 (4.8%) Without PPI: n=5 (3.6%) All bleedings NR	ACS Focus: PPI versus no PPI Severe bleeding defined as intracranial bleeding or any other bleeding leading to hospitalisation and/or red blood transfusion	?	-	-
Yudi 2016 Australia	nRCT Cohort	I: 956 C: 526	N/A	Clinically significant bleeding NR Major bleeding (in-hospital bleeding) n=29 (3.0%) All bleedings NR	Clinically significant bleeding NR Major bleeding (in-hospital bleeding) n=13 (2.5%) All bleedings NR	ACS Major bleeding: based on presentation of in-hospital bleeding defined as bleeding requiring a transfusion and/or associated with a prolonged hospital stay and/or a drop in haemoglobin >3g/dl	?	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Yun 2019 South Korea	nRCT Cohort	PS-matched I: 11,402 C: 11,402	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> 2.5% <u>All bleedings</u> 15.1%	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> 3.1% HR (95% CI): 1.18 (0.98 to 1.43) <u>All bleedings</u> 18.1% HR (95% CI): 1.23 (1.14 to 1.33)	ACS Population extracted from I: 56,216, C: 11,402 Major bleeding defined as fatal bleeding, bleeding necessitating hospitalization, or bleeding in critical sites	?	?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zhao 2020 China	nRCT Cohort	I: 8,520 C: 2,992 *NT-proBNP (ng/L)* *<300* I: 2,874 C: 1,275 *300-1800* I: 3,321 C: 1,130 *>1800* I: 2,325 C: 587	N/A	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> *NT-proBNP:* *<300 ng/L* n=69 (2.4%) *300-1800 ng/L* n=82 (2.5%) *>1800 ng/L* n=81 (3.5%) *All NT-proBNP groups:* n=232 (2.7%) <u>All bleedings</u> *NT-proBNP:* *<300 ng/L* n=193 (6.7%) *300-1800 ng/L* n=227 (6.8%) *>1800 ng/L* n=167 (7.2%) *All NT-proBNP groups:* n=587 (6.9%)	<u>Clinically significant bleeding</u> NR <u>Major bleeding</u> *NT-proBNP:* *<300 ng/L* n=49 (3.8%) aHR (95% CI): 1.02 (0.63 to 1.63) *300-1800 ng/L* n=40 (3.5%) aHR (95% CI): 1.07 (0.66 to 1.73) *>1800 ng/L* n=32 (5.5%) aHR (95% CI): 1.68 (1.03 to 2.74) *All NT-proBNP groups:* n=121 (4.0%) P<0.001, aHR NR <u>All bleedings</u> *NT-proBNP:* *<300 ng/L* n=121 (9.5%) aHR (95% CI): 1.24 (0.97 to 1.60) *300-1800 ng/L* n=109 (9.6%) aHR (95% CI): 1.14 (0.88 to 1.47) *>1800 ng/L* n=65 (11.1%) aHR (95% CI): 1.46 (1.07 to 2.01) *All NT-proBNP groups:* n=295 (9.9%)	STEMI Major bleeding included retroperitoneal bleeding, intracranial bleeding, decline in Hb ≥4 g/dL, transfusion with overt bleeding, bleeding requiring surgical intervention, all during hospitalization All bleeding included all documented bleeding (access-site bleeding, intracranial bleeding, retroperitoneal bleeding, skin or mucosa bleeding, gastrointestinal bleeding, and other sites bleeding) or decline in Hb ≥3 g/dL during hospitalisation	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
					P<0.001, aHR NR				
Zocca 2017 Netherlands	nRCT Historical control	I: 1,009 C: 1,053	N/A	Clinically significant bleeding NR Major bleeding (BARC/TIMI) n=12 (1.2%) All bleedings NR	Clinically significant bleeding NR Major bleeding (BARC/TIMI) n=28 (2.7%) aHR (95% CI): 2.75 (1.34 to 5.61) All bleedings NR	ACS	?	-	?
P2: older ACS patients subjected to DAPT									
RCT									
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	Clinically significant bleeding (PLATO) n=88 (18%) Major bleeding (TIMI) n=9 (2%) All bleedings NR	Clinically significant bleeding (PLATO) n=118 (24%) Major bleeding (TIMI) n=21 (4%) All bleedings NR	NSTE-ACS, ≥70 years	?	+/?	+

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.3
Outcome variable: Bleeding

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Wang 2016a China	RCT Double-blind	I: 100 C: 100	0	Clinically significant bleeding NR Major bleeding (PLATO) n=6 (6%) All bleedings n=14 (14%)	Clinically significant bleeding NR Major bleeding (PLATO) n=8 (8%) All bleedings n=21 (21%)	ACS, ≥65 years of age	-	?	-
nRCT									
Schmucker 2019 Germany	nRCT Cohort	PS-matched I: 238 C: 238	N/A	Clinically significant bleeding Major bleeding NR All bleedings NR	Clinically significant bleeding HR (95% CI): 1.08 (0.49 to 2.37) Major bleeding NR All bleedings NR	STEMI, ≥75 years Population extracted from I: 552, C: 535 patients Clinically significant bleeding included in-hospital bleedings (TIMI major, minor, minimal) and serious bleedings requiring medical attention after discharge	-	-	-
Szummer 2020 Sweden	nRCT Cohort	I: 8,434 C: 5,571	N/A	Clinically significant NR Major bleeding (readmission for bleeding) Incidence: 4.86/100 person-years) All bleedings NR	Clinically significant bleeding NR Major bleeding (readmission for bleeding) Incidence: 6.90/100 person-years aHR (95% CI): 1.48 (1.25 to 1.76) All bleedings NR	AMI, ≥80 years IPTW	+	?	+

*for definitions of bleedings, see main text (page 25)
ACS = acute coronary syndrome, aHR = adjusted hazard ratio, aOR = adjusted odds ratio, BARC = bleeding academic research consortium (clinically significant bleeding: ≥2, major bleeding: ≥3), BMI = body mass index, C = comparison, CABG = coronary artery by-pass grafting, CI = confidence interval, DAPT = dual antiplatelet therapy, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HR = hazard ratio, NR = not reported, I = intervention, IPW = inverse probability weighted, nRCT – not randomized clinical trial, N/A = not applicable, NR = not reported, NSTEMI = non-ST-elevation myocardial infarction, OR = odds ratio, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, PLATO = the pivotal study of platelet inhibition and patient outcome for ticagrelor (clinically significant bleeding: major/minor), PS = propensity score, RCT = randomised clinical trial, sIPTW = stabilized inverse probability of treatment weighting, STEMI = ST-elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction bleeding classification (clinically significant bleeding: major/minor/requiring medical attention), UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Alexopoulos 2015 Greece	RCT Open-label	I: 28 C: 28	0	n=0	n=0	STEMI High platelet reactivity High dose clopidogrel Stent thrombosis not further defined	-	-	-
Cao 2019 China	RCT Open-label	I: 48 C: 49	0	Definite n=0 Definite or probable n=2 (4.2%)	Definite n=0 Definite or probable n=0	STEMI	-	-	-
Gasecka 2020 Poland	RCT Open-label (for clinical data)	I: 30 C: 30	I: 2 C: 3	n=0	n=0	AMI with PCI	-	?	-
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	Definite n=5 (1%)	Definite n=0	NSTE-ACS, ≥70 years	?	+/?	+
Kim 2018 South Korea	RCT Open-label	I: 57 C: 58	I: 17 C: 15	n=0	n=0	AMI Terminated because of slow recruitment Stent thrombosis not further defined	?	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	n=4/281 (1.4%)	n=0/161 (0%)	STEMI Analysis based on patients without switch Stent thrombosis not further defined	-	-	-
Liu 2017 China	RCT Double-blind	I: 87 C: 86	0	Acute or subacute n=0	Acute or subacute n=0	STEMI, diabetes	-	?	-
Liu 2019a China	RCT Open-label	I: 40 C: 40	I: 8 C: 5	n=0	n=0	High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor Stent thrombosis not further defined	-	-	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	n=1 (0.9%)	n=1 (1.1%)	ACS Stent thrombosis not further defined	-	?	-
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	I: 474 C: 474	I: 2 C: 3	Acute n=12 (2.5%) Subacute n=4 (0.8%)	Acute n=3 (0.6%) Subacute n=3 (0.6%)	ACS	?	+/?	-
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	I: 400 C: 400	I: 20 C: 31	Definite n=4 (1%)	Definite n=2 (0.5%)	ACS Analysis included drop-outs	?	+/?	?

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Park 2019b South Korea	RCT Open-label	I: 60 C: 60	0	Definite n=1 (1.7%)	Definite n=0	ACS with PCI	-	?	-
Tang 2016 China	RCT Open-label	I: 210 C: 210	I: 10 C: 10	n=3 (1.5%)	n=0	STEMI Stent thrombosis defined according to the Academic Research Consortium criteria, but presented numbers not further described	-	?	-
Wallentin 2009 Multi-centre	RCT Double-blind	I: 5,649 C: 5,640 (patients with stent)	0	Definite, probable or possible n=202 (3.8%) Definite or probable n=158 (2.9%) Definite n=106 (1.9%)	Definite, probable or possible n=155 (2.9%) Definite or probable n=118 (2.2%) Definite: n=71 (1.3%)	ACS PLATO trial Patient recruitment 2006-2008	?	+	+
Wang 2016b China	RCT Open-label	I: 87 C: 87	0	n=4 (4.6%)	n=0	STEMI, dementia, 60-80 years of age Stent thrombosis not further defined	-	-	-
Wu 2018 China	RCT Open-label	I: 120 C: 124	0	n=0	n=0	ACS Stent thrombosis not further defined	-	?	-
You 2020 China	RCT Open-label	I: 195 C: 105	0	Definite n=1 Definite or probable n=1	Definite n=1 Definite or probable n=2	STEMI, HPR	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zhang 2016 China	RCT Open-label	I: 90 C: 91	0	Definite, probable or possible n=6 (6.7%)	Definite, probable or possible n=0	ACS CYP2C19 poor/intermediate metabolizers High-dose clopidogrel for 7 days, then standard dose	-	-	-
nRCT									
Ahn 2020 South Korea	nRCT Cohort	PS-matched: I: 787 C: 787	N/A	n=10 (1.3%)	n=10 (1.3%) aHR (95% CI): 0.97 (0.40 to 2.34)	AMI with multivessel disease Stent thrombosis not further defined Population extracted from I: 1,438, C:837 patients	?	?	?
Alexopoulos 2016 Greece	nRCT Cohort	I: 959 C: 717	I: 44 C: 31	Urgent revascularisation n=20 (2.1%)	Urgent revascularisation n=14 (2.0)	ACS 75 individuals excluded due to lack of information on vital status	?	-	-
Gajanana 2018 US	nRCT Cohort	I: 1,722 C: 861	N/A	n=2 (0.1%)	n=0	ACS Stent thrombosis not further defined	?	-	-
Gosling 2017 UK	nRCT Cohort	I: 2,880 C: 3,493 PCI-treated patients	N/A	Definite n=33 (1.1%)	Definite n=21 (0.6%)	ACS	?	-	-
Kang 2017 South Korea	nRCT Cohort	I: 6,411 C: 1,708	N/A	Definite, probable n=17 (0.3%)	Definite, probable n=3 (0.2%)	ACS but not CABG	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Krackhardt 2020 Germany	nRCT Cohort	I: 1,549 C: 1,020	N/A	Definite or probable n=8 (0.6%)	Definite or probable n=7 (0.8%) P=0.532	ACS	?	-	-
Ohman 2017 Multi-centre	nRCT (RCT: rivaroxaban versus aspirin)	I: 666 C: 852	N/A	Definite n=4 (0.6%) Definite or probable n=4 (0.6%) Definite, probable or possible n=8 (1.2%)	Definite n=4 (0.5%) Definite or probable n=5 (0.6%) Definite, probable or possible n=8 (0.9%)	ACS	+	-	?
Park 2016 South Korea	nRCT Cohort	PS-matched I: 1,377 C: 1,377	Lost to follow-up at 6 months: I: 249 C: 549	Definite n=9/1,128 (0.8%)	Definite n=6/828 (0.7%) OR (95% CI): 0.872 (0.312 to 2.476)	AMI Excluded patients who switched during hospitalisation Population extracted from I: 6,633, C: 1,377	-	-	-
Rasia 2017 Italy	nRCT Cohort	I: 135 (Plavix), 1,321 (clopidogrel : C: 599	N/A	Plavix: 14.8% Clopidogrel: 6.9%	5.5%	ACS Patients with a medication possession ratio <80 excluded Stent thrombosis not further defined	?	-	-
Sim 2018 South Korea	nRCT Cohort	PS-matched I: 1,553 C: 1,533	N/A	n=13 (0.8%)	n=9 (0.6%) aHR (95% CI): 0.54 (0.22 to 1.35)	Extracted from Korean AMI registry with 13,104 patients Stent thrombosis defined according to the Academic Research Consortium criteria, but presented numbers not further described	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Sim 2019 South Korea	nRCT Cohort	I: 3,180 C: 659	N/A	n=17 (0.5%)	n=2 (0.3%)	NSTEMI Stent thrombosis defined according to the Academic Research Consortium criteria, but presented numbers not further described	-	-	?
Turgeon 2020 Canada	nRCT Cohort	PS-matched I: 3,711 C: 3,711	N/A	n=7 (0.2%)	n=18 (0.5%) HR (95% CI): 2.57 (1.07 to 6.16)	ACS with PCI Stent thrombosis not further defined Population extracted from I: 7,109, C: 4,076 patients	?	+	+
Welsh 2019 Multi-centre	nRCT Cohort	I: 6,500 C: 2,188	N/A	Definite or probable n=128 (2.0%)	Definite or probable n=29 (1.4%)' aHR (95% CI): 1.04 (0.68 to 1.60)	STEMI	?	-	-
Völz 2020 Sweden	nRCT Cohort	I: 12,168 C: 2,929	N/A	Definite n=76 (0.7%)	Definite n=10 (0.4%) aOR (95% CI): 1.18 (0.54 to 2.56)	ACS Instrumental variable 2-stage least squares regression to adjust for confounders	?	?	+
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	n=19 (3.3%) Crude HR (95% CI): 1.036 (0.883-1,642)	n=18 (3.3%)	Recurrent ACS Unclear clopidogrel dose Stent thrombosis not further defined	-	-	-
Zhao 2020 China	nRCT Cohort	I: 8,520 C: 2,992	N/A	n=22 (0.3%)	n=3 (0.1%) P=0.110	STEMI	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.4
Outcome variable: Stent thrombosis

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zocca 2017 Netherlands	nRCT Historic control	I: 1,009 C: 1,053	N/A	Definite n=3 (0.3%) Definite or probable n=6 (0.6%)	Definite n=6 (0.6%) aHR: 1.64 (0.37 to 7.34) Definite or probable n=8 (0.8%) aHR (95% CI): 1.03 (0.33 to 3.27)	ACS	?	-	?
P2: older ACS patients subjected to DAPT									
RCT									
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	I: 506 C: 505	I: 6 C: 3	Definite n=5 (1%)	Definite n=0	NSTE-ACS, ≥70 years	?	+/?	+

ACS = acute coronary syndrome, aHR = adjusted hazard ratio, AMI = acute myocardial infarction, C = comparison, CI = confidence interval, DAPT = dual antiplatelet therapy, HR = hazard ratio, I = intervention, N/A = not applicable, nRCT = non-randomised controlled trial, NSTE-ACS = non-ST-elevation acute coronary syndrome, NSTEMI = non-ST-elevation myocardial infarction, PS = propensity score, RCT = randomised controlled trial, STEMI = ST-elevation myocardial infarction, UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.5
Outcome variable: Angina

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: CS patients subjected to DAPT									
RCT									
Angiolillo 2016 US	RCT Open-label	I: 49 C: 51	I: 1 C: 2	Unstable angina n=3 (6.1%)	Unstable angina n=0	Troponin-negative ACS	-	?	-
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	Rehospitalisation for angina n=64/281 (22.8%)	Rehospitalisation for angina n=9/161 (5.6%)	STEMI Analysis based on patients without switch	-	-	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	Recurrent angina n=9 (8.3%)	Recurrent angina n=2 (2.1%)	ACS	-	?	-
Wu 2018 China	RCT Open-label	I: 120 C: 124	I: 8 C: 5	Recurrent angina n=13 (10.8%)	Recurrent angina n=4 (3.2%)	ACS	-	?	-
Yao 2017 China	RCT Open-label	I: 60 C: 60	0	Recurrent angina n=8 (13.3%)	Recurrent angina n=5 (8.3%)	AMI	-	?	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.5
Outcome variable: Angina

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
nRCT									
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	SAQ Angina stability mean (SD) 65.6 (19.9) Between-group comparison: P<0.001 SAQ Angina frequency mean (SD) 67.8 (20.2) Between-group comparison: P=0.476	SAQ Angina stability mean (SD) 69.6 (21.1) SAQ Angina frequency mean (SD) 66.0 (20.7)	Recurrent ACS Unclear clopidogrel dose Follow-up: 12 months	-	-	-

ACS: acute coronary syndrome, AMI = acute myocardial infarction, C = comparison, DAPT = dual antiplatelet therapy, I = intervention, N/A = not applicable, nRCT = non-randomised controlled trial, RCT = randomised controlled trial, SAQ = Seattle angina questionnaire (score: 0-100, 100=no angina), SD = standard deviation, STEMI = ST-elevation myocardial infarction, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.6
Outcome variable: Rehospitalisation

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Dehghani 2017 Canada	RCT Open-label	I: 68 C: 76	I: 2 C: 2	n=4 (5.8%)	n=2 (2.6%)	STEMI, post-fibrinolytic therapy	?	?	-
Gasecka 2020 Poland	RCT Open-label (for clinical data)	I: 30 C: 30	I: 2 C: 3	n=1	n=1	AMI with PCI	-	?	-
Gu 2017 China	RCT Open-label	I: 36 C: 38	0	Cardiac readmission n=4 (11.1%)	Cardiac readmission n=2 (5.3%)	NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	-	-
Li 2018 China	RCT Open-label	I: 324 C: 329	I: 43 C: 168	Rehospitalisation for angina n=64/281 (22.8%)	Rehospitalisation for angina n=9/161 (5.6%)	STEMI Analysis based on patients without switch	-	-	-
Yang 2018 China	RCT Open-label	I: 60 C: 60	0	n=5 (8.3%)	n=2 (3.3%)	AMI with emergency PCI indication	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.6
Outcome variable: Rehospitalisation

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
nRCT									
Kim 2017 US	nRCT Cohort	PS-matched I: 9,504 C: 2,376	N/A	20.26%	17.75%	ACS, private insurance register Population extracted from I: 22,168, C: 2,524	?	-	-
Welsh 2019 Multi-centre	nRCT Cohort	I: 6,500 C: 2,188	N/A	n=1,053 (16.7%)	n=381 (18.9%)	STEMI	?	-	-
Vyas 2017 US	nRCT Cohort	I: 7,283 C: 1,049	N/A	22.1%	17.1%	ACS Population based on insurance membership	-	-	-

ACS = acute coronary syndrome, AMI = acute myocardial infarction, C = comparison, DAPT = dual antiplatelet therapy, I = intervention, N/A = not applicable, nRCT = non-randomised controlled trial, NSTEMI = non-ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, RCT = randomized controlled trial, STEMI = ST-elevation myocardial infarction, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.7
Outcome variable: Health-related quality of life

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Levin 2013 Multi-centre	RCT Double-blind	I: 8,384 C: 8,462	I: 803 C: 831	EQ-5D Deceased assigned 0: 0.832 Between-group comparison: P=0.046 Deceased excluded: 0.863 Between-group comparison: P=0.69	EQ-5D Deceased assigned 0: 0.840 Deceased excluded: 0.864	ACS Patients from the PLATO trial Patient recruitment 2006-2008	-	?	?
nRCT									
Xin 2019 China	nRCT Cohort	I: 560 C: 523	N/A	SAQ Quality of life mean (SD) 60.9 (24.6) Between-group comparison: P<0.001	SAQ Quality of life mean (SD) 64.2 (23.9)	Recurrent ACS Unclear clopidogrel dose Follow-up: 12 months	-	-	-

ACS = acute coronary syndrome, DAPT = dual antiplatelet therapy, EQ-5D = EuroQol 5 dimensions (0: death; 1 = full health), N/A = not applicable, nRCT = non-randomised controlled trial, RCT = randomised controlled trial, SAQ = Seattle Angina Questionnaire (range: 0-100, high scores indicating better health), SD = standard deviation

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.8
Outcome variable: Dyspnea

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
P1: ACS patients subjected to DAPT									
RCT									
Angiolillo 2016 US	RCT Open-label	I: 49 C: 51	I: 1 C: 2	n=1 (2.0%)	n=2 (3.9%)	Troponin-negative ACS	-	?	-
Berwanger 2019 Multi-centre	RCT Open-label	I: 1,886 C: 1,913	0	n=258 (13.7%)	n=457 (23.9%)	STEMI, post-fibrinolytic therapy, <75 years of age	-	?	-
Cannon 2007 Multi-centre	RCT Double-blind	I: 327 C: 334	0	n=21 (6.4 %)	n=35 (10.5%)	NSTEMI Patient recruitment 2004-2005	-	+	-
Cao 2019 China	RCT Open-label	I: 48 C: 49	0	n=0	n=6 (12.2%)	STEMI	-	-	-
Dehghani 2017 Canada	RCT Open-label	I: 68 C: 76	I: 2 C: 2	n=3 (4.4%)	n=8 (10.5%)	STEMI, post-fibrinolytic therapy	?	?	-
Goto 2015 Multi-centre	RCT Double-blind	I: 380 C: 387 (safety population)	0	n=9 (2.4%)	n= 22 (5.7%)	ACS East-Asian countries	?	+/?	-
Gu 2017 China	RCT Open-label	I: 36 C: 38	0	n=0	n=4 (10.5%)	NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.8
Outcome variable: Dyspnea

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Li 2015 China	RCT Single-blind	I: 24 C: 24	0	n=0	n=3 (12.5%)	High on-treatment platelet reactivity High-dose clopidogrel	-	-	-
Liu 2019a China	RCT Open-label	I: 40 C: 40	I: 8 C: 5	n=0	n=1 (2.8%)	High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor	-	-	-
Lu 2016 China	RCT Open-label	I: 108 C: 95	0	n=0	n=6 (6.3%)	ACS	-	?	-
Park 2019a South Korea	RCT Single-blind	I: 400 C: 400	I: 20 C: 31	n=0	n=7 (1.8%)	ACS Dyspnea as the reason for discontinuation	?	?	?
Park 2019b South Korea	RCT Open-label	I: 60 C: 60	0	n=0	n=0	ACS with PCI Dyspnea as the reason for discontinuation	-	?	-
Wallentin 2009 Multi-centre	RCT Double-blind	I: 9,186 C: 9,235 (safety population)	0	n=721 (7.8%)	n=1,270 (13.8%)	ACS PLATO trial Patient recruitment 2006-2008	?	+	+
Wang 2016b China	RCT Open-label	I: 87 C: 87	0	n=5 (5.57%)	n=12 (13.79%)	STEMI, dementia, 60-80 years of age	-	-	-
Wu 2018 China	RCT Open-label	I: 120 C: 124	I: 8 C: 5	n=0	n=3 (2.4%)	ACS	-	?	-
Xue 2016 China	RCT Double-blind	I: 25 C: 25	I: 5 C: 4	n=0	n=3 (14.3%)	NSTEMI	-	-	-

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 4.8
Outcome variable: Dyspnea

* + No or minor problems
? Some problems
- Major problems

Author year Country	Study design	Patients	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention (clopidogrel)	Control (ticagrelor)				
Zhang 2016 China	RCT Open-label	I: 90 C: 91	0	n=5 (5.6%)	n=15 (16.5%)	ACS CYP2C19 poor/intermediate metabolizers High-dose clopidogrel for 7 days, then standard dose	-	-	-
nRCT									
Alexopoulos 2017 Greece	nRCT Cohort	I: 762 C: 738	I: 37 C: 33	n=53 (7.0%)	n=137 (18.6%) aOR (95% CI): 2.45 (1.85 to 3.23)	ACS Patients not likely to come to follow-up excluded	?	-	+
Turgeon 2020 Canada	nRCT Cohort	PS-matched I: 3,711 C: 3,711	N/A	n=46 (1.2%)	n=116 (3.1%) HR: 2.42 (1.70 to 3.45)	ACS with PCI Population extracted from I: 7,109, C: 4,076 patients	?	+	+
Vyas 2017 US	nRCT Cohort	I: 7,283 C: 1,049	N/A	16.5%	14.5%	ACS Population based on insurance membership	-	-	-

ACS = acute coronary syndrome, aOR = adjusted odds ratio, C = comparison, CI = confidence interval, DAPT = dual antiplatelet therapy, I = intervention, N/A = not applicable, nRCT = non-randomised controlled trial, NSTEMI = non-ST-elevation myocardial infarction, RCT = randomised controlled trial, STEMI = ST-elevation myocardial infarction, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Ahn 2020 South Chorea	nRCT Cohort	?	Asian population, multivessel disease	?	Some imbalance in baseline characteristics Switching not considered Long follow-up for a one-year treatment (2 years)
Alexopoulos 2015 Greece	RCT Open-label	-	STEMI High platelet reactivity High dose clopidogrel Short follow up (during hospital stay)	-	Some imbalance in baseline characteristics High dose clopidogrel
Alexopoulos 2016 Greece	nRCT Cohort	?	Patients not likely to come to follow up excluded	-	Substantial imbalance in baseline characteristics Unclear analysis and handling of switch 75 individuals excluded due to lack of information on vital status
Alexopoulos 2017 Greece	nRCT Cohort	?	Patients not likely to come to follow up excluded	-	Characteristics of I/C groups not reported
Angiolillo 2016 USA	RCT Open-label	-	Low-risk patients: troponin-negative ACS Short follow-up (14 days)	?	Some imbalance in baseline characteristics Bleedings only included if assessed as drug-related, unclear assessment Open-label study (relevant for the assessment of angina)
Antoniou 2018 UK	nRCT Cohort	-	Single center No flow chart provided	-	Treatment allocation depending on risk scores Substantial imbalance in baseline characteristics
Berwanger 2019 Multi-centre	RCT Single-blind (adjudicated endpoints)	-	STEMI, post-fibrinolytic therapy, <75 years of age Information on screening failures lacking	+	
Blin 2019 France	nRCT Cohort	?	Patients who died during hospitalisation or were at rehab afterwards excluded	?	Analysis not considering smoking and socioeconomic factors
Brener 2019 US	nRCT Cohort	?	US register, not described	-	Imbalance in baseline characteristics Unclear handling of cases with switch No protocol, sponsored by industry
Cannon 2007 Multi-centre	RCT Double-blind	-	NSTEMI Patient recruitment 2004-2005 Follow-up: 12 weeks	+	

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Cao 2019 China	RCT Open-label	-	Asian population, single centre, STEMI	-	Some imbalance in baseline characteristics Randomisation procedure according to hospital admission time Unclear collection of outcome data via phone Short follow-up (30 days)
Chang 2020 Taiwan	nRCT Cohort	?	Asian population Low proportion with DES (about 40%)	-	Substantial imbalance in baseline characteristics PS-weighting method not sufficiently described
Choe 2019 South Korea	nRCT Cohort	?	Asian population	-	Some imbalance in baseline characteristics, not statistically significant but systematic (despite PS-matching) No information regarding switch after discharge
De Filippo 2019 Italy	nRCT Cohort	-	2003-2016 No flow chart provided	-	Substantial imbalance in baseline characteristics Baseline characteristics not reported in those with eGFR >60
Dehghani 2017 Canada	RCT Open-label	?	STEMI, post-fibrinolytic therapy Short follow-up (1 month)	?	Some imbalance in baseline characteristics, randomisation procedure not described
Edfors 2018 Sweden	nRCT Cohort	?	Excluded patients without complete data, e.g. creatinine missing (n=4,744)	-	Imbalance at baseline characteristics Different follow up times, later ACS date in the ticagrelor group No protocol, sponsored by industry
Gajanana 2018 US	nRCT Cohort	?	In-hospital stay only Single center	-	Substantial imbalance in baseline characteristics No protocol
Gasecka 2020 Poland	RCT Open-label (for clinical data)	-	High rate of screening failures, reasons not specified for a considerable amount in relation to number of included	?	Some imbalance in baseline characteristics Clinical endpoints not defined
Gimbel 2020 Netherlands	RCT Single-blind (adjudicated endpoints)	?	NSTE-ACS, ≥70years	+/?	Inclusion of 27 patients with prasugrel in the ticagrelor group (5% of all patients in this randomisation group), two patients being discharged with prasugrel High proportion of discontinuations with limited information on treatment after discontinuation

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Giordana 2016 Multi-centre	nRCT Cohort	?	Lack of information on the population included in BleeMACS, only 464 of 8,600 patients in Europe had ticagrelor	-	Focus: Asian versus European population Characteristics of I/C groups not reported
Gosling 2017 UK	nRCT Cohort	?	Single center	-	Substantial imbalance in baseline characteristics Switching not considered
Goto 2015 Multi-centre	RCT Double-blind	?	East-Asian countries	+/?	High discontinuation rate
Grimaldi-Bensouda 2018 France	nRCT Case-control	-	Low proportion of ASA in clopidogrel-group (71% vs 99% in ticagrelor group)	-	Cases and controls differed substantially Switch not considered
Gu 2017 China	RCT Open-label	-	Asian population NSTEMI Clopidogrel non-responders High-dose clopidogrel	-	Unclear randomisation Patients cannot be followed through the study High-dose clopidogrel
Hansson 2016 Sweden	nRCT Cohort	-	ACS with CABG Short follow-up (30 days)	-	Imbalance in baseline characteristics No protocol, sponsored by industry
Jing 2016 China	RCT Open-label	-	Asian population STEMI Short follow-up (during hospitalisation) Reasons for exclusions not provided	-	Lack of information regarding methods Unclear collection of clinical outcomes
Kang 2017 South Korea	nRCT Cohort	-	Asian population Excluded 14% of patients due to incomplete data	-	Substantial imbalance in baseline characteristics Bleeding: Some imbalance between groups, despite PS-matching Information on switching missing
Kim 2017 US	nRCT Cohort	?	Private insurance register	-	Substantial imbalance in baseline characteristics, also in PS-matched cohort Switching not considered,
Kim 2018 South Korea	RCT Open label	?	Asian population Terminated early due to recruitment problems Several patients refused follow-up with OCT	?	High drop-out rate Subjective assessment of outcome (stent thrombosis), sponsored by industry
Kim 2019 South Korea	nRCT Cohort	-	Asian population <75 years of age	-	Substantial imbalance in baseline characteristics Handling of confounders not conceivable

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Krackhardt 2020 Germany	nRCT Cohort	?	Information on screening failures lacking Loading dose unclear	-	Substantial imbalance in baseline characteristics, not considered in analysis
Krishnamurthy 2019 UK	nRCT Cohort	?	UK single centre DES in <50% of clopidogrel patients	-	Substantial imbalance in baseline characteristics Switch after discharge not considered No protocol, industry affiliation
Lee 2018 Taiwan	nRCT Cohort	-	Asian population Subgroup that were not deceased within 30 days	-	Some imbalance in baseline characteristics, despite PS-matching Index date: 30 days after AMI discharge Switch not considered
Levin 2013 Multi-centre	RCT Double-blind	-	Patients from the PLATO trial with HRQL recorded Patient recruitment 2006-2008 EQ-5D does not capture bleedings and dyspnea	?	Little chance to detect differences – 75% had no problems at discharge
Li 2015 China	RCT Single-blind	-	Asian population Single center High on-treatment platelet reactivity High-dose clopidogrel	-	Some imbalance in baseline characteristics Unclear collection of clinical outcomes High-dose clopidogrel
Li 2018 China	RCT Open-label	-	Asian population STEMI Information on screening failures lacking	-	Imbalance in baseline characteristics 48% switch from ticagrelor Deaths in hospital excluded
Liu 2017 China	RCT Double-blind	-	Asian population STEMI, diabetes	?	Some imbalance in baseline characteristics Follow-up of clinical outcomes by phone
Liu 2019a China	RCT Open-label	-	Asian population High on-treatment platelet reactivity High-dose clopidogrel Half-dose ticagrelor	-	Some imbalance in baseline characteristics Large discontinuation rate High-dose clopidogrel Half-dose ticagrelor
Liu 2019b China	RCT Open-label	-	Asian population STEMI, diabetes Unclear recruitment	?	Unclear about discontinuation and adherence Unclear collection of clinical outcomes
Lu 2016 China	RCT Open-label	-	Asian population Low statin dose (rosuvastatin 10 mg), NYHA III and IV excluded	?	Follow-up of clinical outcomes by phone Open-label study (relevant for assessment of angina)

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Mohareb 2020 Egypt	RCT Single-blind (adjudicated endpoints)	?	Single centre, young population	+/?	Some imbalance in baseline characteristics
Ohman 2017 Multi-centre	nRCT	+		-	RCT: rivaroxaban versus aspirin; clopidogrel or ticagrelor was at the discretion of the physician Substantial imbalance in baseline characteristics No protocol, sponsored by industry
Olier 2018 UK	nRCT Cohort	?	STEMI	-	Substantial imbalance in baseline characteristics Unclear analysis Imputation of multiple missing data
Orenes-Pinero 2019 Spain	nRCT Cohort	?	Patients who died during hospitalisation excluded	-	Characteristics of compared groups not reported Large difference between crude and adjusted results
Park 2016 South Korea	nRCT Cohort	-	Asian population AMI Excluded patients who switched during hospitalization	-	Imbalance between compared groups regarding cilastazol Switching after discharge not considered
Park 2019a South Korea	RCT Single-blind (adjudicated endpoints)	?	Asian population	+/?	Some imbalance in baseline characteristics
Park 2019b South Korea	RCT Open-label	-	Asian population, single centre, no information on screening failures	?	Some imbalance in baseline characteristics Lack of information on collection and definition of clinical outcomes
Peyracchia 2020 Switzerland	nRCT Cohort	?	Patient recruitment 2003- Low proportion with DES (about 25%)	?	Exclusion of events during hospitalisation Switching not considered Results presented without CI
Rasia 2017 Italy	nRCT Cohort	?	Patients with a medication possession ratio <80 excluded, numbers not reported	-	Substantial imbalance in baseline characteristics Imbalances not considered in analysis

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	Study design	Problems contributing to downgrading the study in the assessment			
		Directness		Study limitations	
Sahlen 2016 Sweden	nRCT Cohort	?	AMI, not UAP	-	Substantial imbalance in baseline characteristics Unclear handling of switch Imputation of missing data No protocol, industry involvement Outcomes during hospitalisation not included
Schmucker 2019 Germany	nRCT Cohort	-	STEMI, ≥75 years Patient recruitment 2006-	-	Substantial imbalance in baseline characteristics not fully considered in analysis Important factors not reported and considered in PS-matched analysis (Killip class, smoking status, kidney function)
Sheikh Rezaei 2017 Austria	nRCT Cohort	-	Large proportion of exclusions because of death or no prescription within 30 days	-	Substantial imbalance in baseline characteristics Imbalances not considered in analysis No protocol, sponsored by industry
Sim 2018 South Korea	nRCT Cohort	-	Asian population Many exclusions Unclear who are recorded in register	?	Baseline characteristics other than CV factors not reported Switching and discontinuing patients excluded
Sim 2019 South Korea	nRCT Cohort	-	Asian population NSTEMI	-	Substantial imbalance in baseline characteristics Imbalances not considered in analysis PS-matched analysis only provided for P2Y12 blocker versus clopidogrel
Spoendlin 2018 US	nRCT Cohort	-	Diabetes Insurance members	+	
Sun 2019 China	nRCT Cohort	-	Asian population, single centre	?	Some imbalance in baseline characteristics despite PS-matching
Szummer 2020 Sweden	nRCT Cohort	+		?	Unclear handling of confounders in analysis
Tang 2016 China	RCT Open-label	-	Asian population Single center STEMI	?	Limited information on baseline characteristics Short methods section
Turgeon 2020 Canada	nRCT Cohort	?	Low proportion with DES (about 75%)	+	

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Wallentin 2009 Multi-centre	RCT Double-blind	?	Patient recruitment 2006-2008	+	
Wang 2016a China	RCT Double-blind	-	Asian population ≥65 years of age Details on recruitment missing	?	Lack of information regarding methods
Wang 2016b China	RCT Open-label	-	Asian population STEMI, dementia 60-80 years of age	-	Lack of information regarding methods
Wang 2018 China	nRCT Cohort	-	Asian population Single centre	?	Some imbalances between PS-matched groups No information on switch
Wang 2019 China	RCT Open-label	-	Asian population Single center STEMI	?	Some imbalance in baseline characteristics
Welsh 2019 Canada	nRCT Cohort	?	STEMI	-	Substantial imbalance in baseline characteristics Switching not considered
Wu 2018 China	RCT Open-label	-	Asian population Information on screening failures lacking	?	Some imbalance in baseline characteristics
Vyas 2017 US	nRCT Cohort	-	Young population based on insurance membership	-	Substantial imbalance in baseline characteristics Imbalances not considered in analysis No protocol, sponsored by industry
Völz 2020 Sweden	nRCT Cohort	?	Patient recruitment 2005-2015	?	Substantial imbalance in baseline characteristics, unclear handling in analysis Switching not considered No protocol, authors with industry COI
Xin 2019 China	nRCT Cohort	-	Asian population Recurrent MI Many screening failures	-	Some imbalance in baseline characteristics Unclear handling of confounders Unclear clopidogrel dose
Xiong 2015 China	RCT Open-label	-	Asian population Single center CYP2C19 homozygote	-	Unclear medical procedures Unclear clopidogrel dose

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Xue 2016 China	RCT Double-blind	-	Asian population Single center NSTEMI	-	Some imbalance in baseline characteristics Large drop-out: 19% Unclear blinding as tablets were to be halved
Yan 2016 Multi-centre	nRCT Cohort	?	2003-2014 Exclusion of patients due to missing information regarding PPI	-	Analysis focus: PPI vs no PPI Characteristics of I/C groups not reported Unclear handling of confounders
Yang 2018 China	RCT Open-label	-	Asian population Single center Flowchart missing, many patients excluded	-	Limited information on baseline characteristics Unclear collection of outcome data
Yang 2020 China	RCT Open-label	-	Asian population, single centre No flowchart	-	Unclear allocation to treatment groups (retrospective analysis but randomly allocated patients) Limited information on baseline characteristics Unclear collection and definition of outcome data
Yao 2017 China	RCT Open-label	-	Asian population Single center Information on screening failures lacking (120 patients included over 2 years)	?	Limited information on baseline characteristics Unclear collection of outcome data
You 2020 China	RCT Open-label	-	Asian population, STEMI High platelet reactivity	-	Patients with high platelet reactivity on clopidogrel included, patient with high platelet reactivity on ticagrelor excluded Some imbalance in baseline characteristics, randomisation procedure not described
Yudi 2016 Australia	nRCT Cohort	?	Exclusions not described, no flowchart	-	Substantial imbalance in baseline characteristics No information on switching
Yun 2017 South Korea	RCT Open-label	-	Asian population Single center STEMI No screening information	-	Imbalance in baseline characteristics Outcomes restricted to two deaths before SPECT
Yun 2019 South Korea	nRCT Cohort	?	Asian population Follow-up time exceed the usual treatment time of 1 year	?	Complex analysis, difficult to grasp based on the information provided in the publication

Project: Clopidogrel versus ticagrelor in acute coronary syndrome

Appendix 5 Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

Author year Country	**Study design**	**Problems contributing to downgrading the study in the assessment**			
		Directness		**Study limitations**	
Zhang 2016 China	RCT Open-label	-	Asian population CYP2C19 poor/intermediate metabolisers High dose clopidogrel for 7 days, then normal dose	-	Some imbalance in baseline characteristics Unclear collection of outcome data High dose clopidogrel for 7 days, then normal dose
Zhao 2020	nRCT Cohort	-	Asian population STEMI	-	Substantial imbalance in baseline characteristics Switching not considered
Zocca 2017 Netherlands	nRCT Historic control	?	Single centre Exclusions not described	-	Mix of clopidogrel and ticagrelor patients in the compared groups Imbalance in baseline characteristics Adjusted for PS only No protocol, industry involvement

ACS = acute coronary syndrome, AMI = acute myocardial infarction, ASA = acetylsalicylic acid, C = comparison, CABG = coronary artery by-pass grafting, CI = confidence interval, COI = conflict of interest, CV = cardiovascular, DES = drug-eluting stent, eGFR = estimated glomerular filtration rate, HRQL = health-related quality of life, I = intervention, MI = myocardial infarction, NR = not reported, nRCT = non-randomised controlled trial, NSTE-ACS = non-ST-elevation acute coronary syndrome, NSTEMI = non-ST-elevation myocardial infarction, OCT = optical coherence tomography, PAR = platelet aggregation rate, PCI = percutaneous coronary intervention, PPI = proton pump inhibitor, PS = propensity score, RCT = randomised controlled trial, SPECT = single-photon emission computed tomography, STEMI = ST-elevation myocardial infarction, UAP = unstable angina pectoris, UK = United Kingdom, US = United States

Project: Clopidogrel versus ticagrelor in acute coronary syndrome
Appendix 6 Meta-analysis considerations

Meta-analysis methods aim to weight outcome measures from different studies together based on the amount of information per study. This means that the outcome measures need to be defined and estimable for all studies including their weights, normally the standard error. For binary outcomes, the occurrence of study arms with zero events can be in conflict with these requirements.

Having studies with zero events, there are mainly two alternatives. The first alternative is to use continuity correction where 0.5 is added to all four cells (intervention/control * events/non-events). In this HTA, we use the meta-analysis software Revman which automatically applies continuity correction for Relative Risks (RR) and Risk Differences (RD). Revman calculates RR if zero events occur in one study arm, but not if zero events occur in both arms. For RD, Revman accepts zero events in both arms since RD can be calculated also in that situation. However, continuity correction is still needed to estimate the standard error. The continuity correction method is problematic as it adds data that do not exist and introduces a bias, especially if the arms are of different sizes. Further, the standard error for zero-event studies tends to be small and such studies thus receive more weight at the expense of large studies with events recorded.

The second main alternative is to leave zero-event studies out of the analysis. This approach solves the technical issues described above, but it will cause a change in the estimate and can be questioned as some of the available information is disregarded.

In the Table and Figure below, we summarise and illustrate the impact of zero-event RCTs in this HTA.

Table Impact of zero-event RCTs on meta-analysis results in the present HTA. Significant results are bolded.

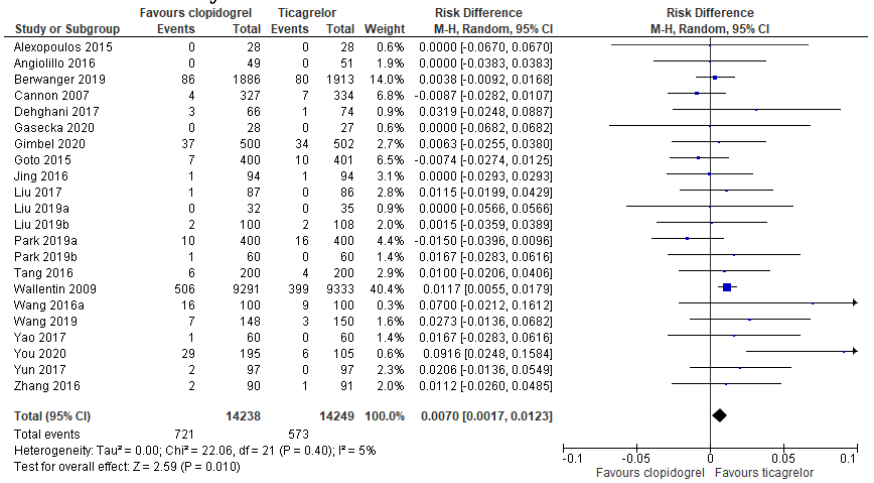
		Meta-analysis	RCTs (n)	Patients (n)	Events	RCTs lost in analysis (n)	Patients lost in analysis (n (%))	Events lost in analysis (n (%))
All-cause mortality	RD, all RCTs	**0.7% (0.2% to 1.2%)**	22	28,487	1,294	-	-	-
	RD, zero-event RCTs excluded	0.5% (-0.3% to 1.4%)	14	27,602	1,289	8	885	5 (0.4)
CV mortality	RD, all RCTs	**0.6% (0.2% to 1.0%)**	26	29,935	1,117	-	-	-
	RD, zero-event RCTs excluded	0.4% (-0.3% to 1.1%)	13	28,327	1,108	13	1,608	9 (0.8)
MI	RD, all RCTs	**0.8% (0.4% to 1.3%)**	28	30,454	1,480	-	-	-
	RD, zero-event RCTs excluded	**0.8% (0.03% to 1.5%)**	17	28531	1,471	11	1,923	9 (0.6)
Clinically significant bleeding	RD, all RCTs	**-1.9% (-3.6% to -0.2%)**	8	25,407	3,162	-	-	-
	RD, zero-event RCTs excluded	**-2.3% (-4.0% to -0.5%)**	7	25,287	3,161	1	120	1 (0.03)
Major bleeding	RD, all RCTs	-0.2% (-0.6% to 0.2%)	26	29,553	1,618	-	-	-
	RD, zero-event RCTs excluded	**-0.8% (-1.5% to -0.03%)**	14	27,775	1,612	12	1,778	6 (0.4)
Stent thrombosis	RD, all RCTs	**0.7% (0.4% to 1.1%)**	18	16,629	225	-	-	-
	RD, zero-event RCTs excluded	**0.6% (0.02% to 1.0%)**	5	13,535	202	13	3,094	23 (10)
Dyspnea	RD, all RCTs	**-6.0% (-7.8% to -4.2%)**	15	25,017	2,870	-	-	-
	RD, zero-event RCTs excluded	**-6.0% (-8.3% to -3.9%)**	8	24,240	2,844	7	777	26 (0.9)

CV = cardiovascular, MI = myocardial infarction, RCT = randomised controlled trial, RD = risk difference

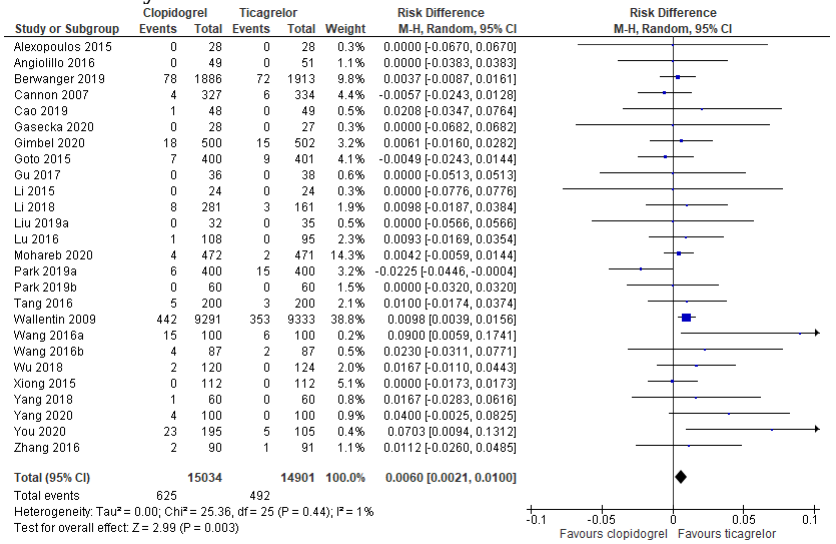
Figure Forest plots of meta-analyses with and without zero-event RCTs

All RCTs

All-cause mortality

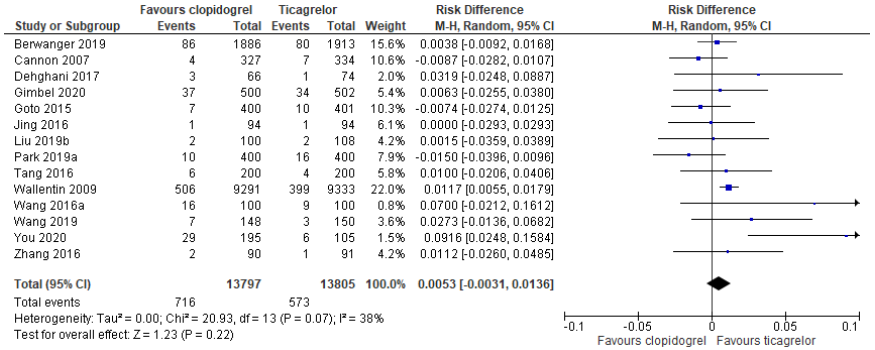


CV mortality

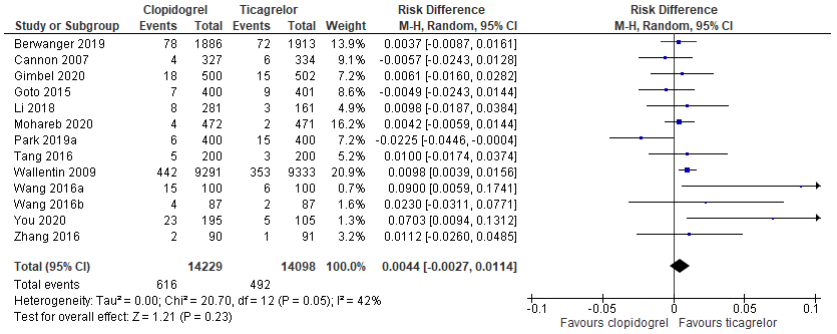


RCTs without zero-event arm

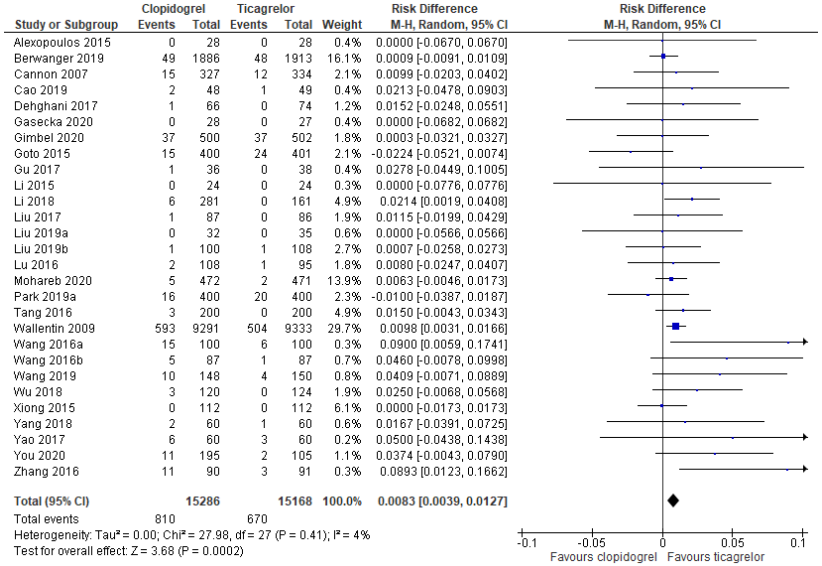
All-cause mortality

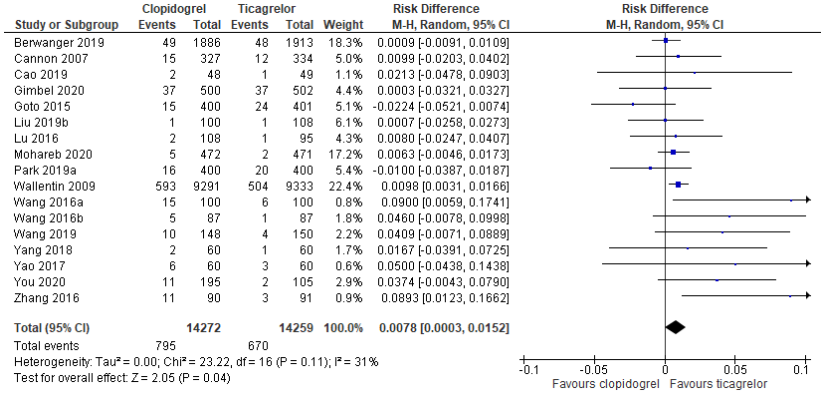


CV mortality

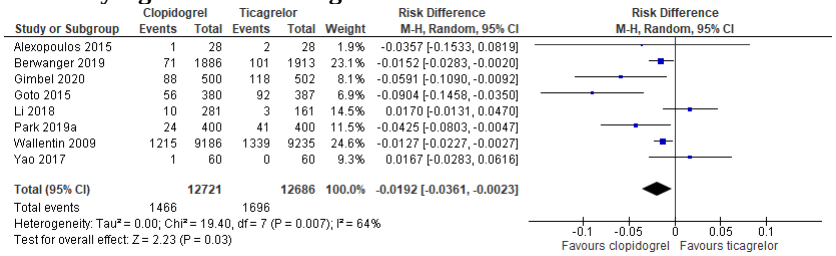


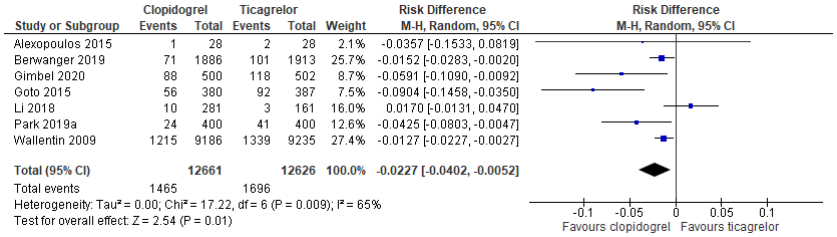
MI



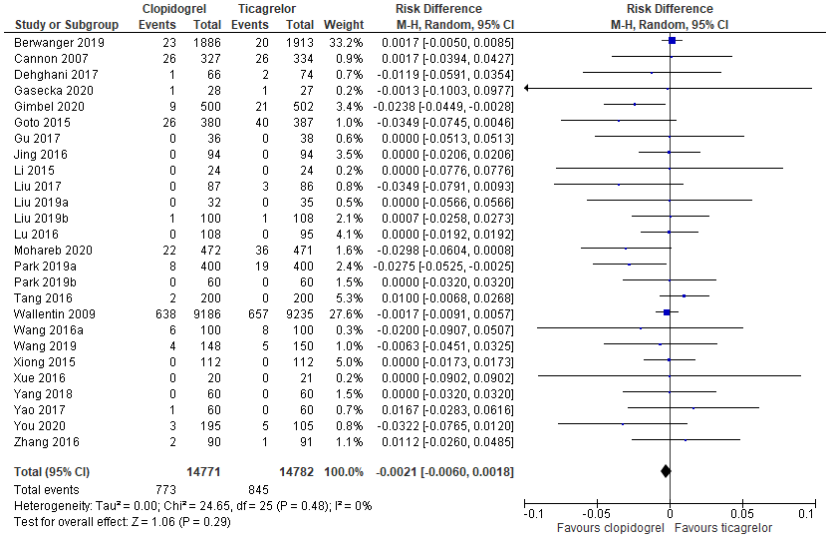


Clinically significant bleeding





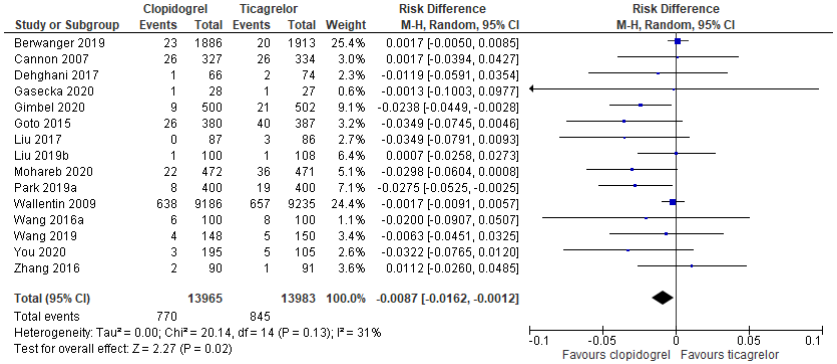
Major bleeding



Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Berwanger 2019	23	1886	20	1913	33.2%	0.0017 [-0.0050, 0.0085]
Cannon 2007	26	327	26	334	0.9%	0.0017 [-0.0394, 0.0427]
Dehghani 2017	1	66	2	74	0.7%	-0.0119 [-0.0591, 0.0354]
Gasecka 2020	1	28	1	27	0.2%	-0.0013 [-0.1003, 0.0977]
Gimbel 2020	9	500	21	502	3.4%	-0.0238 [-0.0449, -0.0028]
Goto 2015	26	380	40	387	1.0%	-0.0349 [-0.0745, 0.0046]
Gu 2017	0	36	0	38	0.6%	0.0000 [-0.0513, 0.0513]
Jing 2016	0	94	0	94	3.5%	0.0000 [-0.0206, 0.0206]
Li 2015	0	24	0	24	0.2%	0.0000 [-0.0776, 0.0776]
Liu 2017	0	87	3	86	0.8%	-0.0349 [-0.0791, 0.0093]
Liu 2019a	0	32	0	35	0.5%	0.0000 [-0.0566, 0.0566]
Liu 2019b	1	100	1	108	2.1%	0.0007 [-0.0258, 0.0273]
Lu 2016	0	108	0	95	4.1%	0.0000 [-0.0192, 0.0192]
Mohareb 2020	22	472	36	471	1.6%	-0.0298 [-0.0604, 0.0008]
Park 2019a	8	400	19	400	2.4%	-0.0275 [-0.0525, -0.0025]
Park 2019b	0	60	0	60	1.5%	0.0000 [-0.0320, 0.0320]
Tang 2016	2	200	0	200	5.3%	0.0100 [-0.0068, 0.0268]
Wallentin 2009	638	9186	657	9235	27.6%	-0.0017 [-0.0091, 0.0057]
Wang 2016a	6	100	8	100	0.3%	-0.0200 [-0.0907, 0.0507]
Wang 2019	4	148	5	150	1.0%	-0.0063 [-0.0451, 0.0325]
Xiong 2015	0	112	0	112	5.0%	0.0000 [-0.0173, 0.0173]
Xue 2016	0	20	0	21	0.2%	0.0000 [-0.0902, 0.0902]
Yang 2018	0	60	0	60	1.5%	0.0000 [-0.0320, 0.0320]
Yao 2017	1	60	0	60	0.7%	0.0167 [-0.0283, 0.0616]
You 2020	3	195	5	105	0.8%	-0.0322 [-0.0765, 0.0120]
Zhang 2016	2	90	1	91	1.1%	0.0112 [-0.0260, 0.0485]
Total (95% CI)		**14771**		**14782**	**100.0%**	**-0.0021 [-0.0060, 0.0018]**
Total events	773		845			

Heterogeneity: Tau² = 0.00; Chi² = 24.65, df = 25 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)

Risk Difference M-H, Random, 95% CI
-0.1 -0.05 0 0.05 0.1
Favours clopidogrel Favours ticagrelor

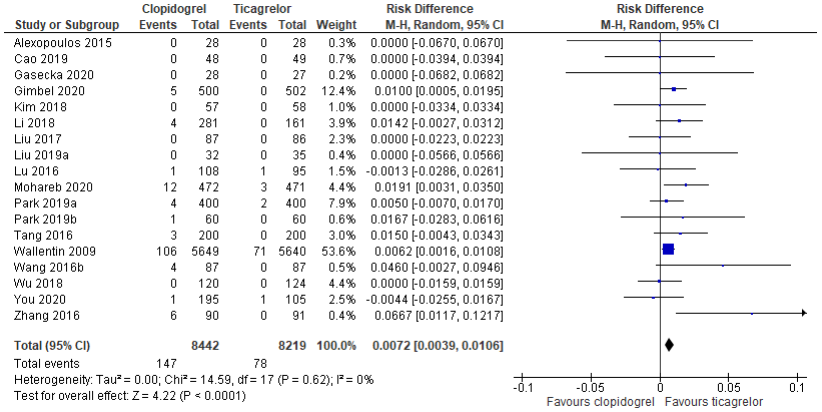


Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Berwanger 2019	23	1886	20	1913	25.4%	0.0017 [-0.0050, 0.0085]
Cannon 2007	26	327	26	334	3.0%	0.0017 [-0.0394, 0.0427]
Dehghani 2017	1	66	2	74	2.3%	-0.0119 [-0.0591, 0.0354]
Gasecka 2020	1	28	1	27	0.6%	-0.0013 [-0.1003, 0.0977]
Gimbel 2020	9	500	21	502	9.1%	-0.0238 [-0.0449, -0.0028]
Goto 2015	26	380	40	387	3.2%	-0.0349 [-0.0745, 0.0046]
Liu 2017	0	87	3	86	2.7%	-0.0349 [-0.0791, 0.0093]
Liu 2019b	1	100	1	108	6.4%	0.0007 [-0.0258, 0.0273]
Mohareb 2020	22	472	36	471	5.1%	-0.0298 [-0.0604, 0.0008]
Park 2019a	8	400	19	400	7.1%	-0.0275 [-0.0525, -0.0025]
Wallentin 2009	638	9186	657	9235	24.4%	-0.0017 [-0.0091, 0.0057]
Wang 2016a	6	100	8	100	1.1%	-0.0200 [-0.0907, 0.0507]
Wang 2019	4	148	5	150	3.4%	-0.0063 [-0.0451, 0.0325]
You 2020	3	195	5	105	2.6%	-0.0322 [-0.0765, 0.0120]
Zhang 2016	2	90	1	91	3.6%	0.0112 [-0.0260, 0.0485]
Total (95% CI)		**13965**		**13983**	**100.0%**	**-0.0087 [-0.0162, -0.0012]**
Total events	770		845			

Heterogeneity: Tau² = 0.00; Chi² = 20.14, df = 14 (P = 0.13); I² = 31%
Test for overall effect: Z = 2.27 (P = 0.02)

Risk Difference M-H, Random, 95% CI
-0.1 -0.05 0 0.05 0.1
Favours clopidogrel Favours ticagrelor

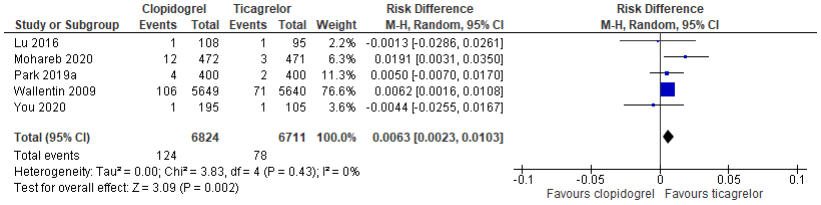
Stent thrombosis



Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Alexopoulos 2015	0	28	0	28	0.3%	0.0000 [-0.0670, 0.0670]
Cao 2019	0	48	0	49	0.7%	0.0000 [-0.0394, 0.0394]
Gasecka 2020	0	28	0	27	0.2%	0.0000 [-0.0682, 0.0682]
Gimbel 2020	5	500	0	502	12.4%	0.0100 [0.0005, 0.0195]
Kim 2018	0	57	0	58	1.0%	0.0000 [-0.0334, 0.0334]
Li 2018	4	281	0	161	3.9%	0.0142 [-0.0027, 0.0312]
Liu 2017	0	87	0	86	2.3%	0.0000 [-0.0223, 0.0223]
Liu 2019a	0	32	0	35	0.4%	0.0000 [-0.0566, 0.0566]
Lu 2016	1	108	1	95	1.5%	-0.0013 [-0.0286, 0.0261]
Mohareb 2020	12	472	3	471	4.4%	0.0191 [0.0031, 0.0350]
Park 2019a	4	400	2	400	7.9%	0.0050 [-0.0070, 0.0170]
Park 2019b	1	60	0	60	0.6%	0.0167 [-0.0283, 0.0616]
Tang 2016	3	200	0	200	3.0%	0.0150 [-0.0043, 0.0343]
Wallentin 2009	106	5649	71	5640	53.6%	0.0062 [0.0016, 0.0108]
Wang 2016b	4	87	0	87	0.5%	0.0460 [-0.0027, 0.0946]
Wu 2018	0	120	0	124	4.4%	0.0000 [-0.0159, 0.0159]
You 2020	1	195	1	105	2.5%	-0.0044 [-0.0255, 0.0167]
Zhang 2016	6	90	0	91	0.4%	0.0667 [0.0117, 0.1217]
Total (95% CI)		**8442**		**8219**	**100.0%**	**0.0072 [0.0039, 0.0106]**
Total events	147		78			

Heterogeneity: Tau² = 0.00; Chi² = 14.59, df = 17 (P = 0.62); I² = 0%
Test for overall effect: Z = 4.22 (P < 0.0001)

Risk Difference M-H, Random, 95% CI
-0.1 -0.05 0 0.05 0.1
Favours clopidogrel Favours ticagrelor

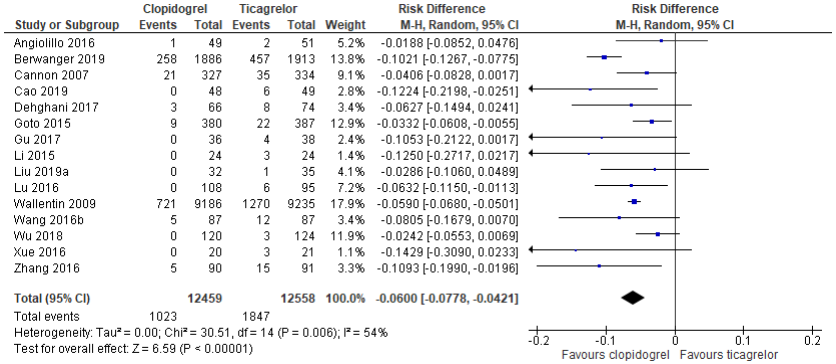


Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Lu 2016	1	108	1	95	2.2%	-0.0013 [-0.0286, 0.0261]
Mohareb 2020	12	472	3	471	6.3%	0.0191 [0.0031, 0.0350]
Park 2019a	4	400	2	400	11.3%	0.0050 [-0.0070, 0.0170]
Wallentin 2009	106	5649	71	5640	76.6%	0.0062 [0.0016, 0.0108]
You 2020	1	195	1	105	3.6%	-0.0044 [-0.0255, 0.0167]
Total (95% CI)		**6824**		**6711**	**100.0%**	**0.0063 [0.0023, 0.0103]**
Total events	124		78			

Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)

Risk Difference M-H, Random, 95% CI
-0.1 -0.05 0 0.05 0.1
Favours clopidogrel Favours ticagrelor

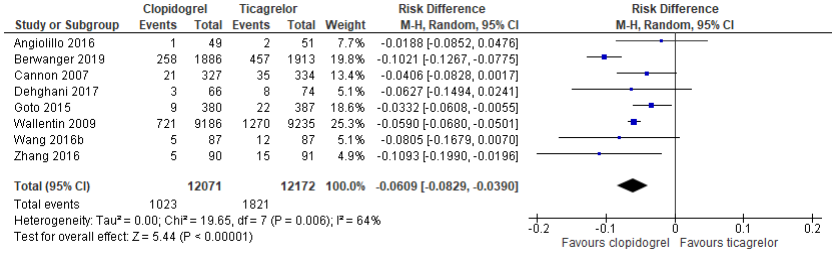
Dyspnea



Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Angiolillo 2016	1	49	2	51	5.2%	-0.0188 [-0.0852, 0.0476]
Berwanger 2019	258	1886	457	1913	13.8%	-0.1021 [-0.1267, -0.0775]
Cannon 2007	21	327	35	334	9.1%	-0.0406 [-0.0828, 0.0017]
Cao 2019	0	48	6	49	2.8%	-0.1224 [-0.2198, -0.0251]
Dehghani 2017	3	66	8	74	3.4%	-0.0627 [-0.1494, 0.0241]
Goto 2015	9	380	22	387	12.9%	-0.0332 [-0.0608, -0.0055]
Gu 2017	0	36	4	38	2.4%	-0.1053 [-0.2122, 0.0017]
Li 2015	0	24	3	24	1.4%	-0.1250 [-0.2717, 0.0217]
Liu 2019a	0	32	1	35	4.1%	-0.0286 [-0.1060, 0.0489]
Lu 2016	0	108	6	95	7.2%	-0.0632 [-0.1150, -0.0113]
Wallentin 2009	721	9186	1270	9235	17.9%	-0.0590 [-0.0680, -0.0501]
Wang 2016b	5	87	12	87	3.4%	-0.0805 [-0.1679, 0.0070]
Wu 2018	0	120	3	124	11.9%	-0.0242 [-0.0553, 0.0069]
Xue 2016	0	20	3	21	1.1%	-0.1429 [-0.3090, 0.0233]
Zhang 2016	5	90	15	91	3.3%	-0.1093 [-0.1990, -0.0196]
Total (95% CI)		**12459**		**12558**	**100.0%**	**-0.0600 [-0.0778, -0.0421]**
Total events	1023		1847			

Heterogeneity: Tau² = 0.00; Chi² = 30.51, df = 14 (P = 0.006); I² = 54%

Test for overall effect: Z = 6.59 (P < 0.00001)



Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Ticagrelor Events	Ticagrelor Total	Weight	Risk Difference M-H, Random, 95% CI
Angiolillo 2016	1	49	2	51	7.7%	-0.0188 [-0.0852, 0.0476]
Berwanger 2019	258	1886	457	1913	19.8%	-0.1021 [-0.1267, -0.0775]
Cannon 2007	21	327	35	334	13.4%	-0.0406 [-0.0828, 0.0017]
Dehghani 2017	3	66	8	74	5.1%	-0.0627 [-0.1494, 0.0241]
Goto 2015	9	380	22	387	18.6%	-0.0332 [-0.0608, -0.0055]
Wallentin 2009	721	9186	1270	9235	25.3%	-0.0590 [-0.0680, -0.0501]
Wang 2016b	5	87	12	87	5.1%	-0.0805 [-0.1679, 0.0070]
Zhang 2016	5	90	15	91	4.9%	-0.1093 [-0.1990, -0.0196]
Total (95% CI)		**12071**		**12172**	**100.0%**	**-0.0609 [-0.0829, -0.0390]**
Total events	1023		1821			

Heterogeneity: Tau² = 0.00; Chi² = 19.65, df = 7 (P = 0.006); I² = 64%

Test for overall effect: Z = 5.44 (P < 0.00001)

Components of this Health Technology Assessment

- ☑ Description of methods
- ☑ PICO
- ☑ Full literature search
- ☑ Flowchart
- ☑ Selection based on relevance
- ☑ Quality assessment
- ☑ Data tabulation
- ☑ Evidence synthesis
- ☑ Meta-analysis
- ☑ Certainty of evidence by GRADE
- ☑ Summary
- ☑ Economical aspects
- ☑ Organisational aspects
- ☑ Ethical aspects
- ☑ Ongoing studies
- ☑ Excluded articles
- ☑ Participation of experts
- ☑ External review
- ☑ Knowledge gaps identified
- ☑ Conflict of interest reported

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Sahlgrenska Universitetssjukhuset, HTA-centrum
Röda Stråket 8, 413 45 Göteborg
www.sahlgrenska.se/htacentrum