Risk of infections in patients treated with ticagrelor versus clopidogrel: a systematic review and meta-analysis

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Abstract

Aims: Ticagrelor has been shown to reduce the risk of pneumonia and improve lung function, but the findings across studies were inconsistent. The objective is to investigate the relative safety of ticagrelor versus clopidogrel on infection outcomes in patients with cardiovascular diseases.

Methods and results: We searched MEDLINE, EMBASE, Cochrane Library, and *ClinicalTrials.gov* up to 15 October 2019. Randomized controlled trials comparing ticagrelor and clopidogrel that reported infection outcomes were included. The primary outcome was pneumonia. Secondary outcomes were upper respiratory tract infection (URTI), urinary tract infection (UTI) and sepsis. Study quality was assessed using the Cochrane Risk of Bias tool. Study selection, data extraction and quality assessment were conducted by independent authors. Random-effects model was used for data synthesis. Relative risks (RRs) and 95% confidence intervals (CIs) were pooled with a random-effects model. Out of 5231 citations, ten trials with altogether 37514 patients were included. Ticagrelor was associated with a lower risk of pneumonia (RR 0.80, 95% CI 0.67 to 0.95) compared to clopidogrel. There were no statistically significant differences for URTI (RR 0.71, 95% CI 0.34 to 1.48), UTI (RR 1.06, 95% CI 0.73 to 1.64), or sepsis (RR 0.79, 95% CI 0.50 to 1.26).

Conclusions: Compared to clopidogrel, ticagrelor reduces the risk of pneumonia, but not URTI, UTI or sepsis. Our study provides further evidence for recommending ticagrelor to patients with acute coronary syndrome at risk of pneumonia, although the mechanism by which ticagrelor reduces the risk of pneumonia merits further research.

Keywords: Ticagrelor; Clopidogrel; Pneumonia; Infections; Meta-analysis

Introduction

Cardiovascular diseases (CVDs) are the leading causes of mortality and morbidity worldwide. [1,2] P2Y12 inhibitors, such as clopidogrel and ticagrelor, are effective in preventing myocardial infarction, stroke and cardiovascular death. [3] Both European and US guidelines recommend the use of ticagrelor, together with aspirin as dual antiplatelet therapy, in patients with acute coronary syndrome after percutaneous coronary intervention (ST-segment elevation myocardial infarction or non-ST-segment elevation acute coronary syndrome) to improve cardiovascular outcomes, although at a cost of higher risk of bleeding compared to clopidogrel; while clopidogrel is preferred for patients with stable coronary artery diseases undergoing percutaneous coronary intervention. [4-7] So far, these recommendations were made mainly based on the evidence about their effects on cardiovascular outcomes and bleeding, while other outcomes, such as infections, which are not rare and could be life-threatening, have been much less addressed. [8,9]

Oral P2Y12 inhibitors are believed to increase the risk of infections. [3] Previous cohort studies showed that clopidogrel increased the risk of infections by 48% [8] to 51% [9] compared to placebo. This is supported by findings from both *in vitro* and *in vivo* studies. [10] Interestingly, ticagrelor, but not clopidogrel, has been suggested to have protective effects against infections. The Platelet Inhibition and Patient Outcomes (PLATO) trial showed that patients treated with ticagrelor had a lower risk of pneumonia and death due to pneumonia and sepsis than clopidogrel. [11,12] In a randomized trial of patients with pneumonia, ticagrelor reduced thrombo-inflammatory biomarkers, improved lung function, and reduced the need for supplemental oxygen. [13] Moreover, ticagrelor had a protective effect on renal function in sepsis-induced acute kidney injury mice models. [14] Recent *in vivo* and *in vitro* studies have revealed its antibacterial and other anti-infection effects. [15,16]

Nevertheless, the comparison between ticagrelor and clopidogrel in terms of infection outcomes yielded inconsistent findings. A *post hoc* analysis of the PLATO trial [11] showed that ticagrelor significantly reduced the risk of infections, but this effect was not statistically significant in the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial [17]. Furthermore, some trials observed reverse association in that the patients on ticagrelor had a higher risk of pneumonia, pharyngitis, upper respiratory tract infection (URTI) and urinary tract infection (UTI). [18,19] However, their sample sizes were small. It remains uncertain whether the inconsistencies were due to small sample size, patient characteristics, specific infection types, or chance. Therefore, the objective of this systematic review and meta-analysis was to compare the effect of ticagrelor versus clopidogrel on common infection outcomes (pneumonia, URTI, UTI and sepsis) in patients with CVDs at baseline.

Methods

This systematic review and meta-analysis was conducted and reported in accordance with the recommendations of the Cochrane Handbook (Version 5.1.0) [20] and the PRISMA statement [21]. This study was registered on PROSPERO (CRD42020154506).

Literature search

We conducted a literature search in EMBASE, MEDLINE, Cochrane library and *ClinicalTrials.gov* for eligible studies through 15 October 2019. The following keywords and their synonyms were used: (1) ticagrelor (Brilinta, Brilique, Possia), (2) clopidogrel (Plavix), and (3) randomized controlled trial. The search strategy is shown in Appendix 1. The reference lists of eligible studies and relevant reviews were also manually searched for additional studies.

Study selection and data extraction

We included randomized controlled trials that compared ticagrelor with clopidogrel in adult patients (aged ≥ 18 years) with CVDs and reported outcome data for infections. The baseline CVDs included but not limited to acute coronary syndrome, stroke, angina, myocardial infarction and peripheral artery diseases. The primary outcome was pneumonia, while secondary outcomes included URTI, UTI and sepsis. There were no restrictions on treatment duration, follow-up time, sample size, and whether using ticagrelor or clopidogrel alone or being used in dual antiplatelet therapy with aspirin. We excluded studies that included immunocompromised (e.g. HIV) and immunosuppressed patients. When multiple studies were found to be based on the same trial, we included the one with the biggest eligible sample size or longest follow-up period; sample size was prioritized over follow-up length, when the study with the biggest sample size and the study with the longest follow-up period were different. All the inclusion and exclusion criteria were specified prior to literature search and screening. The titles and abstracts of all retrieved citations were first screened to assess their potential eligibility, and final eligibility was determined after examining their full texts.

Data extraction and quality assessment

We extracted the following information using a pre-designed data extraction form: bibliographic information (author, year of publication), study information (trial name, trial registration number, country, sample size), patient characteristics (age, proportion of male patients, baseline CVDs, comorbidities, surgical procedures), treatment information (regimen, dose, treatment duration) and outcome data (event number for each outcome, follow-up time). Since we only included randomized trials and all outcomes of interest were binary, we extracted the original 2*2 table for each outcome. When a trial included multiple arms of the same drug but at different doses, we combined them into one single drug arm. For example,

we combined two arms of ticagrelor at 45 mg and 90 mg twice daily [22] into one single ticagrelor arm and comparing it with the clopidogrel arm. This method is recommended in the Cochrane Handbook [20] and adopted in previous systematic reviews. [23] Many studies did not report data on infection outcomes of interest in their journal-published reports, in which case we examined their *ClinicalTrials.gov* webpages for more information or contacted the corresponding authors by e-mail.

We extracted other information necessary for the assessment of methodological quality. The Cochrane Collaboration's tool for assessing risk of bias was used to assess methodological quality. [24] This tool evaluated potential bias from seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The risk of bias was judged as high, low or unclear in each domain, and the overall risk of bias was judged based on the risks in all seven domains, as low when all domains were judged as low, as high when any domains were judged as high, or as unclear otherwise.

Study selection, data extraction and quality assessment were conducted by three independent authors (QF, HLL and MFT). Any disagreement was resolved by discussion until consensus was reached or by consulting a fourth author.

Data analysis

The clopidogrel arm was used as the reference in all the analyses. Intention-to-treat analysis was employed. Relative risks (RR) and their 95% confidence intervals (CI) were estimated from the extracted 2*2 table for each outcome and then pooled across studies to obtain an overall effect estimate by using a random-effects model with inverse variance weighting. RR

> 1 would favor clopidogrel, otherwise ticagrelor. Subgroup analysis was prespecified for pneumonia based on baseline CVD type, therapy type (monotherapy versus dual therapy), treatment duration (< 12 months versus ≥ 12 months). Subgroup analyses were also performed based on the proportion of diabetic patients in each trial (≥ 30% versus < 30%) because diabetic patients are generally at higher risk of infections,[25] and 30% was the median proportion of diabetic patients in all included studies. Sensitivity analysis was performed by excluding studies with a high risk of bias and by using odds ratio (OR) as the effect measure. Statistical heterogeneity across studies was measured by the I^2 statistic and Cochrane's Q test. An I^2 > 50% or a p-value < 0.10 was suggestive of substantial heterogeneity, in which case meta-regression would be used to investigate potential sources of heterogeneity. Publication bias was investigated with funnel plot, but Egger's test for asymmetry in funnel plot would be performed only when the number of eligible studies was ten or more, because it would generate misleading results otherwise. [20,26] Asymmetries in the funnel plot by visual assessment or a p-value for Egger's test < 0.10 would suggest potential publication bias, and the trim-and-fill method would be employed to adjust for potential bias. [27] The statistical significance level was decided at 0.05 unless specified otherwise. All data analyses were performed with the *"meta"* package in R software (Version 3.4.3).

Results

Among the 5231 citations identified by literature search, 10 trials [17-19,22,28-33] with altogether 37514 patients (18790 on ticagrelor and 18724 on clopidogrel) were considered eligible (Figure 1). The mean age was 62.7 (range 58.7 to 67.0) years old, and 76.8% (range 70.0% to 89.2%) patients were males. The median sample size was 105.5 (range 36 to 18624). The median proportion of diabetes was 29.8% (range 16.8% to 52.5%). The median proportion of current or previous smokers was 52.5% (range 35.8% to 77.9%) (Table 1). Eight trials enrolled patients

from multiple centers. [17,18,22,28-31,33] Patients had acute coronary syndrome in four trials, [18,19,28,29] stable coronary disease in three trials, [22,30,33] peripheral artery disease in one trial, [17] myocardial infarction in one trial, [31] and coma with cardiac arrest and percutaneous coronary intervention in one trial. [32] Ticagrelor and clopidogrel were often used in dual antiplatelet therapy with aspirin, but used alone in three trials. [17,19,33] The trials encompassed a wide range of treatment duration, from 2 days to 30 months with a median of 42 days. Four trials had a follow-up period of 12 months or longer. [17,28,29,31] Four trials included more than 30% of the study patients with baseline diabetes. [17,18,28,33] More baseline characteristics are shown in Appendix 2. According to the Cochrane Collaboration's tool for assessing risk of bias, five out of the ten trials had an overall high risk of bias, due to their open-label design. [18,19,31-33] The other five trials had low risk of bias (Appendix 3). [17,22,28-30]

Seven studies with altogether 37228 patients reported data on pneumonia. The RRs ranged from 0.32 to 3.20. Overall, ticagrelor was associated with a 20% risk reduction in pneumonia compared to clopidogrel (RR 0.80, 95% CI 0.67 to 0.95) (Figure 2(A)). Prespecified subgroup analyses demonstrated that ticagrelor significantly reduced the risk of pneumonia when it was used for ≥ 12 months (RR 0.80, 95% CI 0.67 to 0.96), in dual therapy (RR 0.73, 95% CI 0.55 to 0.96), and in patients with acute coronary syndrome (RR 0.72, 95% CI 0.53 to 0.98), although the difference between subgroups did not reach the prespecified significance level of 0.05, mainly due to the wide confidence intervals of the other subgroup(s) (Table 2). Since the PLATO and the EUCLID trials contributed more than 90% of total weight and might drive the overall effect, we conducted a sensitivity analysis removing these two trials, which yielded an overall RR 0.79 (95% CI 0.42 to 1.48). The point estimate was very close to the primary analysis, although the CI became wider due to the smaller sample size.

Seven trials with 33579 patients, four trials with 33333 patients and two trials with 32466 patients reported the outcome of URTI, UTI and sepsis, respectively. By pooling results across studies, we did not find that ticagrelor reduced risk of URTI (RR 0.71, 95% CI 0.34 to 1.48), UTI (RR 1.09, 95% CI 0.73 to 1.64), or sepsis (RR 0.79, 95% CI 0.50 to 1.26) (Figure 2(B) – (D)).

The heterogeneity in all these meta-analyses ranged from no to low. Sensitivity analyses by excluding trials with a high risk of bias yielded similar results to the primary analyses (Appendix 4). Substituting RR with OR produced similar results: OR 0.79 (95% CI 0.66 to 0.95) for pneumonia, 0.70 (95% CI 0.33 to 1.49) for URTI, 1.09 (95% CI 0.73 to 1.65) for UTI, and 0.79 (95% CI 0.50 to 1.26) for sepsis. Subgroup analyses based on diabetic status showed no subgroup difference in the effect of ticagrelor on pneumonia (RR 0.83 (95% CI 0.66 to 1.04) versus 0.74 (95% CI 0.55, 1.01) for diabetic and non-diabetic patients, respectively, p for subgroup difference = 0.55), URTI (RR 0.47 (95% CI 0.13 to 1.65) versus 0.79 (95% CI 0.31 to 2.01), p = 0.51), UTI (RR 1.09 (95% CI 0.56 to 2.15) versus 1.31 (95% CI 0.72 to 2.38), p = 0.70)) and sepsis (RR 1.01 (95% CI 0.55 to 1.84) versus 0.63 (95% CI 0.34 to 1.15), p = 0.28). Symmetry was observed in the funnel plots for pneumonia, URTI and sepsis, but not for UTI (Appendix 5). Since the numbers of eligible studies for all outcomes were below 10, we did not test for publication bias formally as explained in Methods. Trim-and-fill method generated an overall RR of 0.98 (95% CI 0.66 to 1.46) for UTI.

Discussion

In this systematic review and meta-analysis of ten trials with 37514 CVD patients, we found that patients treated with ticagrelor had a lower risk of pneumonia, but not of URTI, UTI or

sepsis, compared with clopidogrel. To our knowledge, this is the first systematic review and meta-analysis that addresses this research question.

The PLATO trial [29] was the first study revealing the protective effect of ticagrelor on infection outcomes, in which patients treated with ticagrelor were at a lower risk of pulmonary adverse effects and related death but not of sepsis, URTI or UTI. These findings were consistent with our results. However, the PLATO trial was the only one that showed a protective effect of ticagrelor against pneumonia, [29] while the other trials failed to show a significant effect, which may be due to reasons such as small size, short follow-up or insufficient events. Two trials even suggested an association in the opposite direction [19,31]. Our study is of great value in resolving the inconsistencies across studies and provides more reliable evidence. The *post hoc* analysis of the PLATO trial [11] revealed that ticagrelor reduced the risk of pulmonary adverse effects by 17% (RR 0.83, 95% CI 0.71 to 0.97; computed from extracted data). However, dyspnea, which counted as a pulmonary adverse effect, is more common in patients treated with ticagrelor compared to clopidogrel. [34] Ticagrelor's effect on reducing pneumonia might therefore be more than 17%. In PLATO, the reduction in pneumonia was 29% (RR 0.71, 95% CI 0.53 to 0.98; as shown in Figure 2(A)). In our meta-analysis, the overall risk reduction in pneumonia was around 20%.

The primary use of ticagrelor and clopidogrel, as P2Y12 inhibitors, is protection against cardiovascular events through platelet inhibition. [35] Inhibition of platelets has downstream effects on inflammation and immunity, such as reducing platelet release of pro-inflammatory alpha-granule contents and the formation of pro-inflammatory platelet-leukocyte aggregates. [10] These features lead to a potentially higher risk of infection, as demonstrated by previous cohort studies of clopidogrel. [8,9]. As a more potent platelet-inhibitor than clopidogrel, the

protective effect of ticagrelor on infection outcomes was unlikely to be due to its platelet-inhibition function. This hypothesis is also supported by the observation that clopidogrel and prasugrel had similar effects on infection outcomes despite their difference in platelet-inhibition efficacy. [36]

Unlike clopidogrel, ticagrelor can additionally inhibit cellular uptake of adenosine via inhibiting the equilibrative nucleoside transporter 1 (ENT1) receptor, [37] which increases intracellular levels of adenosine. Adenosine has been shown to activate neutrophils to release cytokines, chemokines, and arachidonic acid-derived lipid mediators, to promote neutrophil chemotaxis, phagocytosis and degranulation via low-affinity G protein-coupled receptors A_{2A} and A_{2B} at high concentration and play a role in the resolution of lung injury [16,38-41]. Lancelloti *et al*. showed that ticagrelor also has a direct anti-microbial effect on multiple gram-positive bacteria strains *in vitro*, which is not seen in other P2Y12 inhibitors. [15] Ticagrelor inhibited biofilm growth and dissemination to surrounding tissues in *Staphylococcus aureus*-infected mice at conventional dosage. [15] Ticagrelor has also been believed to have a promising role in preventing multi-organ failure among patients with sepsis due to resistant gram-positive *cocci*. [42] These are the two potential mechanisms by which ticagrelor reduces pulmonary infections, but more research is needed.

Previous studies have focused on ticagrelor's effect on preventing pneumonia and improving lung function, [11,13] but few on its effect on other infections. Currently, there is no evidence of a reduction in infections in the upper respiratory tract or urinary tract. Pneumonia is usually due to Gram-positive pathogens, whereas URTI is usually caused by virus, and UTI and septicemia are usually caused by Gram-negative bacteria. Therefore, our findings are actually

in line with Lancelloti *et al*.'s finding [15] that ticagrelor has anti-microbial effects on Gram-positive bacteria, rather than other bacteria strains.

We found that ticagrelor showed a significant protective effect when used in dual therapy, for a long duration, and in patients with acute coronary syndrome, which is consistent with the recommended usage in current guidelines. [5,6] Aspirin in dual therapy is not known to be associated with the risk of infection, and so it can be combined with ticagrelor as dual therapy. [43,44] Ticagrelor is preferred over clopidogrel in the management of ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome, especially for those undergoing percutaneous coronary intervention. [5,6,45] Although current recommendations on the usage of dual antiplatelet therapy were made mainly based on ticagrelor's efficacy regarding cardiovascular outcomes and safety regarding bleeding, [45] they are now further supported by our findings that ticagrelor could provide patients with the additional benefit of reducing pneumonia risk.

Three randomized trials compared ticagrelor with placebo in patients with baseline CVDs: stable coronary disease and diabetes in the THEMIS trial, [46] acute stroke or transient ischemic attack in the SOCRATES trial, [47] and previous heart attack in the PEGASUS trial. [48] All three trials consistently showed that ticagrelor tended to reduce the risk of pneumonia, although the results did not reach statistical significance. Combining them using meta-analysis yielded similar results (RR 0.91 (95% CI 0.77 to 1.07), Appendix 6); the lack of significance could be attributed to the low number of pneumonia cases in these studies. This finding seems also consistent with ticagrelor's antibacterial effect *in vitro* and *in vivo*, [15] however, future studies with larger sample size or longer follow-up are required for confirmation. Therefore, physicians may consider ticagrelor as the preferred therapy for eligible acute coronary

syndrome patients undergoing percutaneous coronary intervention and at high risk of pneumonia, such as the elderly, the bedbound, smokers, and COPD patients. Moreover, polymorphisms in CYP2C19 can cause variability in a patient's response to clopidogrel, which is a prodrug that requires activation. [49] Ticagrelor does not have this issue.

Since pneumonia and CVDs are both leading causes of morbidity and mortality in the elderly, dual antiplatelet therapy with ticagrelor should be further recommended to eligible patients because it is effective in reducing the risk of both conditions. In people over the age of 65 years in the general population, the incidence of pneumonia ranges from 25 to 44 per 1000 person-year, [50] higher than that in the PLATO trial (10.2 per 1000 person-year) and the EUCLID trials (9.5 per 1000 person-year). This is because the trials tend to exclude patients that are very old. Translating the relative effect (RR = 0.80) into absolute effect using a baseline incidence of 10 per 1000 person-year, the 10-year risk difference is 2.0% and the number needed to treat is 50, meaning that treating 50 eligible patients with ticagrelor would prevent one case of pneumonia in 10 years. However, when using the baseline incidence of 44 (or 25) per 1000 person-year, the 10-year risk difference and the number needed to treat are 8.8% (or 5.0%) and 12.5 (or 20), respectively.

Some limitations have to be acknowledged in this study. First, we only included studies published in English, which might cause selection bias. Second, we did not perform Egger's test for examining asymmetry in funnel plots. Egger's test would give misleading results in the case of a small number of eligible studies (< 10), and is therefore not recommended. The funnel plots are shown in Appendix 5. Third, we did not include the outcome of infection-related mortality, which is clinically more important but rarely reported in randomized trials. The PLATO trial showed that ticagrelor and clopidogrel had a similar risk of infection-related death,

[12] but more data are required for conducting a meta-analysis. Although the effect on pneumonia-related mortality remains unknown, pneumonia *per se* can cause substantial disease burdens and decreased quality of life. Fourth, the results of prespecified subgroup analyses did not reach statistical significance. Although we recommend long-term use of ticagrelor in dual therapy in acute coronary syndrome, we could not conclude that ticagrelor did not have an effect in treatment duration < 12 months, in patients with other conditions than acute coronary syndrome, or in monotherapy. More studies are required to explore its potential clinical applications. Fifth, the PLATO and the EUCLID trials contributed disproportionately large weights in the meta-analysis of pneumonia, but the sensitivity analysis by removing them generated similar point estimates although wider confidence intervals. Sixth, the two big trials included, PLATO and EUCLID, had long follow-up periods (12 months and 30 months, respectively), which made it difficult to identify whether other factors that may have occurred during follow-up that would affect the final results. Seventh, this study was conducted with summary data instead of individual patient data, which prevented us from performing more flexible subgroup analysis or regression. Eighth, the studies included in this meta-analysis were randomized controlled trials that were not specifically designed with infection as the primary outcome, and so were underpowered to allow firm conclusions on infection risk. Future randomized controlled trials investigating infections as the prespecified outcome are warranted. Ninth, more epidemiological evidence is required to judge whether ticagrelor *per se* reduces the risk of pneumonia compared to placebo.

Conclusion

This meta-analysis found that compared to clopidogrel, ticagrelor reduces the risk of pneumonia, but not URTI, UTI or sepsis. This further supports the guideline-recommended use of ticagrelor with aspirin in dual antiplatelet therapy in the management of patients with acute coronary syndrome undergoing percutaneous coronary intervention, especially in those with a

high risk of pneumonia. However, further research is needed to confirm the causality and investigate the mechanism of this protective effect.

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Figure legends

Figure 1: Flowchart of study selection

Figure 2: Forest plots of comparing ticagrelor with clopidogrel regarding infection outcomes (A) Pneumonia, (B) URTI, (C) UTI, and (D) Sepsis

URTI: Upper respiratory tract infection. UTI: Urinary tract infection.

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1459-544.

2. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE),

1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1603-58.

3. Kipshidze N, Platonova E, DiNicolantonio JJ, Kuliczkowski W, Serebruany VL. Excessive long-term platelet inhibition with prasugrel or ticagrelor and risk of infection: another hidden danger? *Am J Ther* 2015;22(2):e22-7.

4. Briasoulis A, Telila T, Palla M, Siasos G, Tousoulis D. P2Y12 receptor antagonists: which one to choose? A systematic review and meta-analysis. *Curr Pharm Des* 2016;22(29):4568-76.

5. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* 2016;134(10):e123-55.

6. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Jüni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group, ESC Committee for Practice Guidelines (CPG), ESC National Cardiac Societies. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The

Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018 14;39(3):213–60.

7. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy: JACC Guideline Comparison. *J Am Coll Cardiol*. 2018 11;72(23 Pt A):2915–31.

8. Gross AK, Dunn SP, Feola DJ, Martin CA, Charnigo R, Li Z, Abdel-Latif A, Smyth SS. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. *J Thromb Thrombolysis* 2013;35(2):147-54.

9. Blasco-Colmenares E, Perl TM, Guallar E, Baumgartner WA, Conte JV, Alejo D, Pastor-Barriuso R, Sharrett AR, Faraday N. Aspirin plus clopidogrel and risk of infection after coronary artery bypass surgery. *Arch Intern Med* 2009;169(8):788-96.

10. Thomas MR, Storey RF. Effect of P2Y12 inhibitors on inflammation and immunity. *Thromb Haemost* 2015;114(3):490-7.

11. Storey RF, James SK, Siegbahn A, Varenhorst C, Held C, Ycas J, Husted SE, Cannon CP, Becker RC, Steg PG, Asenblad N, Wallentin L. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. *Platelets* 2014;25(7):517-25.

12. Varenhorst C, Alstrom U, Braun OO, Storey RF, Mahaffey KW, Bertilsson M, Cannon CP, Scirica BM, Himmelmann A, James SK, Wallentin L, Held C. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. *Heart* 2014;100(22):1762-9.

13. Sexton TR, Zhang G, Macaulay TE, Callahan LA, Charnigo R, Vsevolozhskaya OA, Li Z, Smyth S. Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. *JACC Basic Transl Sci* 2018;3(4):435-49.

14. Li X, Li Y, Shen K, Li H, Bai J. The protective effect of ticagrelor on renal function in a mouse model of sepsis-induced acute kidney injury. *Platelets* 2019;30(2):199-205.

15. Lancellotti P, Musumeci L, Jacques N, Servais L, Goffin E, Pirotte B, Oury C. Antibacterial activity of ticagrelor in conventional antiplatelet dosages against antibiotic-resistant Gram-positive bacteria. *JAMA Cardiol* 2019;4(6):596-99.

16. Alsharif KF, Thomas MR, Judge HM, Khan H, Prince LR, Sabroe I, Ridger VC, Storey RF. Ticagrelor potentiates adenosine-induced stimulation of neutrophil chemotaxis and phagocytosis. *Vascul Pharmacol* 2015;71:201-7.

17. Hiatt WR, Fowkes FG, Heizer G, Berger JS, Baumgartner I, Held P, Katona BG, Mahaffey KW, Norgren L, Jones WS, Blomster J, Millegard M, Reist C, Patel MR, EUCLID Trial Steering Committee Investigators. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med* 2017;376(1):32-40.

18. Angiolillo DJ, Franchi F, Waksman R, Sweeny JM, Raveendran G, Teng R, Zhao Y, Carlson G, Khan N, Mehran R. 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.

19. Chen Y. A phase IV study of the onset and maintenance of the antiplatelet effect of ticagrelor compared with clopidogrel in Chinese patients with ACS (NCT01864005): ClinicalTrials.gov; 2015 [Available from: https://clinicaltrials.gov/ct2/show/record/NCT01864005] accessed October 2019.

20. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0) [updated March 2011]: The Cochrane Collaboration 2011.

21. 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.

22. Hiasa Y, Teng R, Emanuelsson H. Pharmacodynamics, pharmacokinetics and safety of ticagrelor in Asian patients with stable coronary artery disease. *Cardiovasc Interv Ther* 2014;29(4):324-33.

23. Feng Q, Zhou A, Zou H, Ingle S, May MT, Cai W, Cheng CY, Yang Z, Tang J. Quadruple versus triple combination antiretroviral therapies for treatment naive people with HIV: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2019;366:l4179.

24. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

25. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: A matched cohort study. *Dia Care*. 2018 Mar;41(3):513–21.

26. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol* 2000;53(5):477-84.

27. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-63.

28. Goto S, Huang CH, Park SJ, 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.

29. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington

RA, PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361(11):1045-57.

30. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS, Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* 2009;120(25):2577-85.

31. Berwanger O, Lopes RD, Moia DDF, Fonseca FA, Jiang L, Goodman SG, Nicholls SJ, Parkhomenko A, Averkov O, Tajer C, Malaga G, Saraiva JFK, Guimaraes HP, Barros ESPGM de, Damiani LP, Santos RHN, Paisani DM, Miranda TA, Valeis N, Piegas LS, Granger CB, White HD, Nicolau JC. Ticagrelor versus clopidogrel in patients with STEMI treated With fibrinolysis: TREAT trial. *J Am Coll Cardiol* 2019;73(22):2819-28.

32. Steblovnik K, Blinc A, Mijovski MB, Fister M, Mikuz U, Noc M. Ticagrelor versus clopidogrel in comatose survivors of out-of-hospital cardiac arrest undergoing percutaneous coronary intervention and hypothermia: a randomized study. *Circulation* 2016;134(25):2128-30.

33. Price MJ, Clavijo L, Angiolillo DJ, Carlson G, Caplan R, Teng R, Maya J. A randomised trial of the pharmacodynamic and pharmacokinetic effects of ticagrelor compared with clopidogrel in Hispanic patients with stable coronary artery disease. *J Thromb Thrombolysis* 2015;39(1):8-14.

34. Parodi G, Storey RF. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor. *Eur Heart J Acute Cardiovasc Care* 2015;4(6):555-60.

35. McFadyen JD, Schaff M, Peter K. Current and future antiplatelet therapies: emphasis on preserving haemostasis. *Nat Rev Cardiol* 2018;15(3):181-91.

36. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;357(20):2001-15.

37. Sumaya W, Storey RF. Ticagrelor: effects beyond the P2Y12 receptor. *Interv Cardiol Clin* 2017;6(1):49-55.

38. Jacobson KA, Gao ZG. Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov* 2006;5(3):247-64.

39. Hasko G, Cronstein B. Regulation of inflammation by adenosine. *Front Immunol* 2013;4:85.

40. Barletta KE, Ley K, Mehrad B. Regulation of neutrophil function by adenosine. *Arterioscler Thromb Vasc Biol* 2012;32(4):856-64.

41. Inoue Y, Chen Y, Hirsh MI, Yip L, Junger WG. A3 and P2Y2 receptors control the recruitment of neutrophils to the lungs in a mouse model of sepsis. *Shock* 2008;30(2):173-7.

42. Jean SS, Hsueh SC, Hwang JJ, Hsueh PR. Ticagrelor: A promising role in preventing multi-organ failure among patients with sepsis due to resistant gram-positive cocci. *J Microbiol Immunol Infect*. 2019;52(4):513–5.

43. Hsu J, Donnelly JP, Chaudhary NS, Moore JX, Safford MM, Kim J, Wang HE. Aspirin use and long-term rates of sepsis: A population-based cohort study. *PLoS ONE*. 2018 Apr 18;13(4):e0194829.

44. Harrak H, Normand I, Grinker R, Elftouh N, Laurin LP, Lafrance JP. Association between acetylsalicylic acid and the risk of dialysis-related infections or septicemia among incident hemodialysis patients: a nested case-control study. *BMC Nephrol*. 2015 Jul 28;16:115.

45. Fei Y, Tsoi MF, Cheung TT, Cheung BM. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of randomized controlled trials. *Int J Cardiol*. 2016 Oct 1;220:895–900.

46. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstrale W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalan R, Cornel JH, Widimsky P, Leiter LA, THEMIS Steering Committee Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med*. 2019 Oct 3;381(14):1309–20.

47. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS, SOCRATES Steering Committee Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med*. 2016 Jul 7;375(1):35–43.

48. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, Magnani G, Bansilal S, Fish MP, Im K, Bengtsson O, Oude Ophuis T, Budaj A, Theroux P, Ruda M, Hamm C, Goto S, Spinar J, Nicolau JC, Kiss RG, Murphy SA, Wiviott SD, Held P, Braunwald E, Sabatine MS, PEGASUS-TIMI Steering Committee Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015 May 7;372(19):1791–800.

49. Siasos G, Zaromitidou M, Oikonomou E, Vavuranakis M, Tsigkou V, Papageorgiou N, Chaniotis D, Vrachatis DA, Stefanadis C, Papavassiliou AG, Tousoulis D. Genetics in the clinical decision of antiplatelet treatment. *Curr Pharm Des*. 2017;23(9):1307–14.

50. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, Restrepo MI. The management of community-acquired pneumonia in the elderly. *Eur J Intern Med*. 2014 Apr;25(4):312–9.

Table 1: Basic characteristics of eligible studies

Study ID	ClinicalTrials.gov identifier	Trial period	Male %	Age (mean)	CVD	STE-ACS %	Diabetes %	Smoker %	Sample size (ticagrelor/ clopidogrel)	Ticagrelor regimen	Clopidogrel regimen	Treatment duration	Risk of bias
EUCLID	NCT01732822	2012-2016	72	66	PAD	0.0	38.5	77.9	6910/6932	Ticagrelor 90 mg bid	Clopidogrel 75 mg once daily	30 months	Low
PLATO	NCT00391872	2006-2009	71.7	62	ACS	37.6	25.0	35.8	9333/9291	Ticagrelor 180 mg as loading and 90mg bid + aspirin 75/100mg	Clopidogrel 300 mg as loading and 75mg once daily + aspirin 75/100 mg	12 months	Low
TREAT	NCT02298088	2015-2017	77.1	58.9	MI	100.0	16.8	66.0	1913/1886	Ticagrelor 180 mg as loading and 90mg bid + aspirin 75/100mg	Clopidogrel 300 mg as loading and 75mg once daily + aspirin 75/100 mg	12 months	High
PHILO	NCT01294462	2011-2012	76.5	67	ACS	51.8	34.6	38.3	387/380	Ticagrelor 180 mg as loading and 90 mg bid + aspirin 75/100 mg daily	Clopidogrel 300 mg as loading and 75mg once daily + aspirin 75/100 mg	12 months	Low
Angiolillo 2016	NCT01603082	2012-2014	70	61.4	ACS	0.0	36.0	NA	51/49	Ticagrelor 180 mg as loading	Clopidogrel 600 mg as loading	14 days	High
Steblovnik 2016	NCT02224274	2014-2016	83.3	62	coma survivor with cardiac arrest	77.8	NA	NA	20/16	ticagrelor 180 mg as loading and 90 mg bid	clopidogrel 600 mg as loading and 75mg once daily + aspirin 100 mg	2 days	High
Chen 2015	NCT01864005	2013-2014	82.5	58.7	ACS	47.7	NA	NA	29/31	Ticagrelor 180 mg as loading and 90 mg bid	Clopidogrel 600 mg as loading and 75mg once daily + aspirin 100 mg	6 weeks	High
ONSET/ OFFSET	NCT00528411	2007-2009	75.6	63.8	SCAD	0.0	19.8	NA	57/54	Ticagrelor 180 mg as loading and 90 mg bid + aspirin 75/100 mg daily	Clopidogrel 600 mg as loading and 75mg once daily + aspirin 75/100 mg	6 weeks	Low
Price 2015	NCT01523366	2012-2013	70	63.8	SCAD	0.0	52.5	NA	40/39	Ticagrelor 180 mg as loading and 90 mg bid + aspirin 75/100 mg daily	Clopidogrel 600 mg as loading and 75mg once daily + aspirin 75/100 mg	7 days	High

Hiasa 2014	NCT01118325	2010-2011	89.2	63	SCAD	0.0	24.6	NA	50/46	Ticagrelor 45/90 mg bid + aspirin 75/100 mg daily	Clopidogrel 75mg once daily + aspirin 75/100 mg	4 weeks	Low

PAD: peripheral artery disease. ACS: acute coronary syndrome. STE-ACS: ST-segment elevation acute coronary syndrome. MI: myocardial infarction. SCAD: stable coronary artery disease. NA: not available.

Table 2: Results of subgroup analyses for pneumonia.

Subgroups	Study N	Sample N	RR (95% CI)	P value for subgroup difference
Overall	7	37228	0.80 (0.67, 0.95)	NA
Treatment duration				
< 12 months	3	196	0.73 (0.35, 1.51)	0.81
≥12 months	4	37032	0.80 (0.67, 0.96)	
Therapy type				
Monotherapy	2	13902	0.84 (0.67, 1.06)	0.41
Dual Therapy	5	23326	0.73 (0.55, 0.96)	
Baseline CVD				
ACS	4	19551	0.72 (0.53, 0.98)	0.77
MI	1	3799	1.31 (0.29, 5.87)	
PAD	1	13842	0.70 (0.32, 1.52)	
Comatose with cardiac arrest	1	36	0.84 (0.67, 1.05)	

CVD: cardiovascular disease. PAD: peripheral artery disease. MI: myocardial infarction.

ACS: acute coronary syndrome; NA: not applicable.

Figure 1: PRISMA flow chart

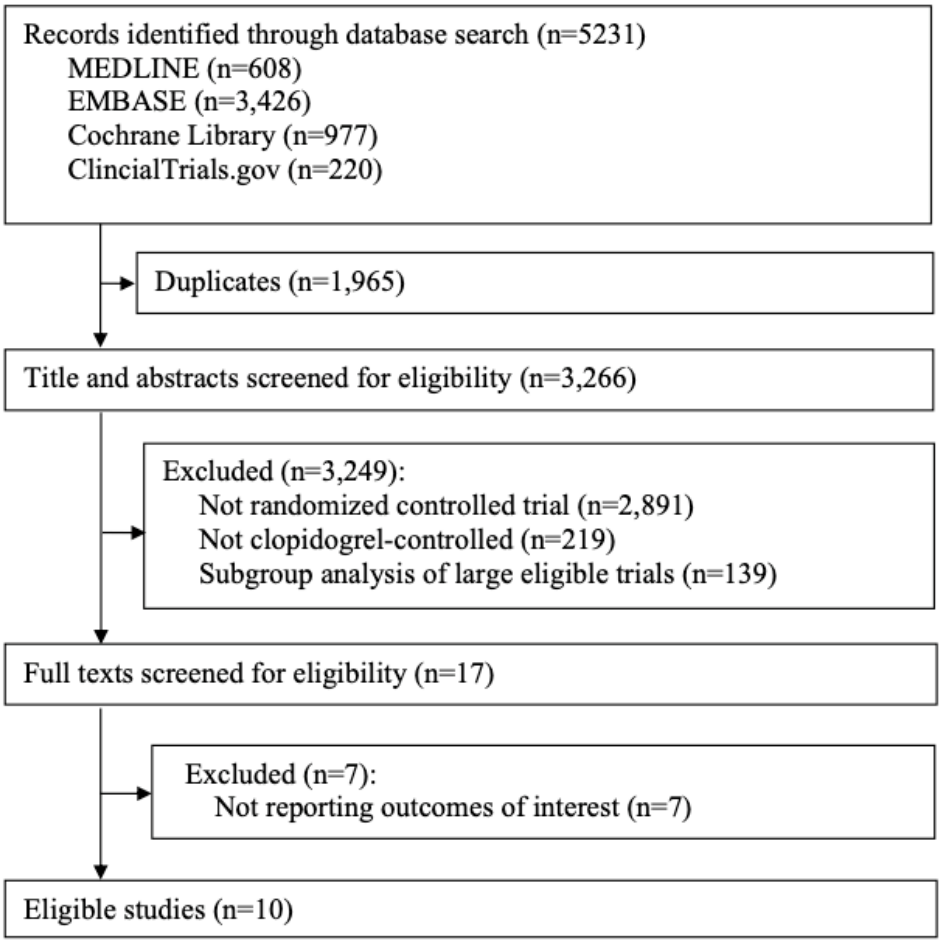
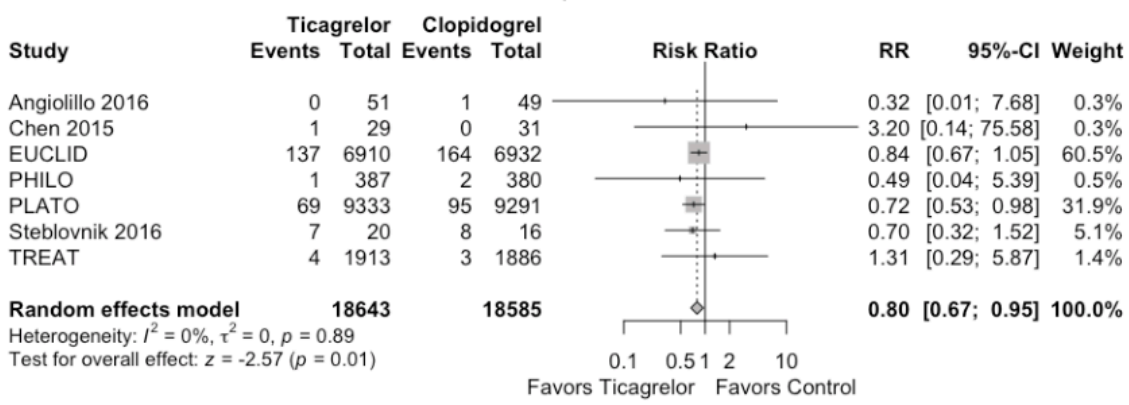
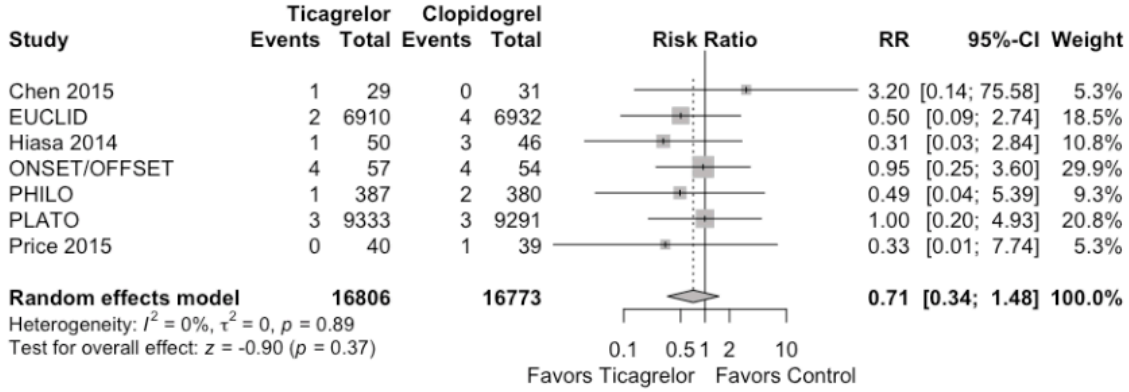


Figure 2: Forest plots

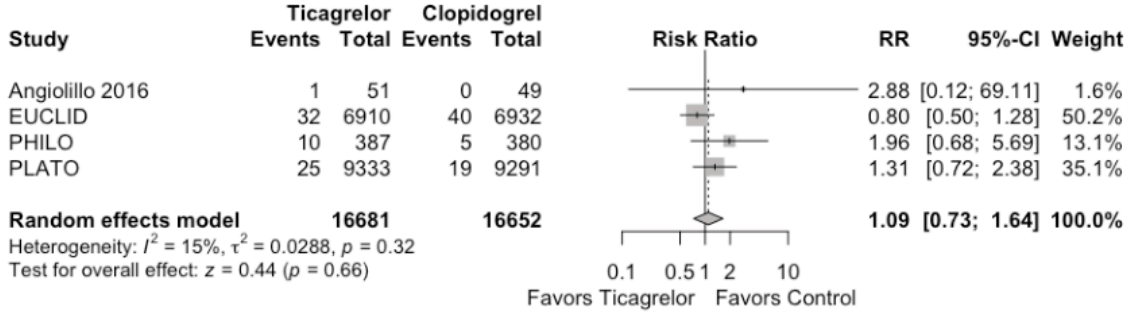
(A) Pneumonia



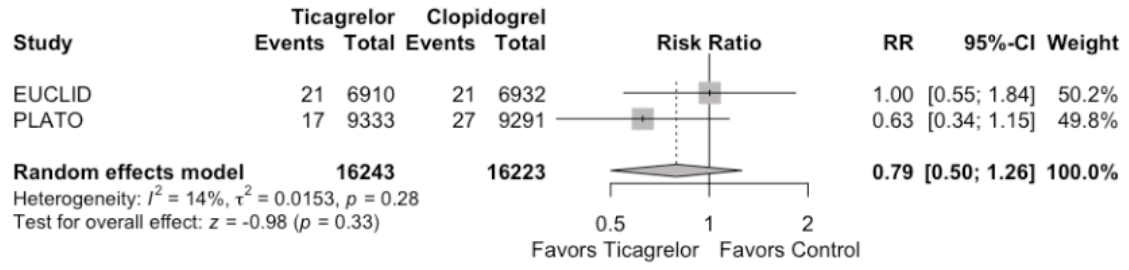
(B) URTI



(C) UTI



(D) Sepsis



Appendices

Appendix 1: Search strategy

Appendix 2: Baseline characteristics of the included trials (supplementary)
Part (A) basic characteristics, (B) comorbidities, (C) comorbidities (continued), (D) baseline/pre-randomization non-study/concurrent medications.

Appendix 3: Results of quality assessment

Appendix 4: Results of sensitivity analysis by excluding studies with high risk of bias (A) pneumonia, (B) URTI, (C) UTI, (D)sepsis

Appendix 5: Funnel plots for meta-analyses
(A) pneumonia, (B) URTI, (C) UTI, (D)sepsis

Appendix 6: Forest plot of the meta-analysis comparing ticagrelor versus placebo

Appendix 1: Search strategy

#1. '*ticagrelor*' OR '*brilique*' OR '*brilinta*' OR '*possia*' OR '*AZD6140*' OR '*AZD 6140'* OR '*AZD-6140'*

#2. '*clopidogrel*' OR '*clopidogrel sandoz*' OR '*clopidogrel mepha'* OR '*clopidogrel-mepha'* OR '*iscover*' OR '*Plavix*' OR '*clopidogrel napadisilate'* OR '*clopidogrel hydrochloride'* OR '*clopidogrel besylate'* OR '*clopidogrel besilate'* OR '*clopidogrel bisulfate'* OR '*PCR 4099'* OR '*PCR-4099'*

#3. '*randomized*' OR '*randomised*' OR '*random**' OR '*randomization*' OR '*randomisation*'

#4. #1 AND #2 AND #3

Appendix 2: Baseline characteristics of the included trials (supplementary)

Part A: basic characteristics (ticagrelor arm vs. clopidogrel arm)

Study ID	Age, years	Female	Body weight, kg	BMI, kg/m2	Race			Current and/or previous smoker
					White	Black	Asian	
Angiolillo 2016	≥65 years: 15(29.4) vs 19(38.8)	17(33.3) vs 13(26.5)	NA	≥30 kg/m^2: 24(48.0) vs 24(49.0)	33(71.7) vs 33(71.7)	11(23.9) vs 11(23.9)	1(2.0) vs 2(4.1)	NA
Chen 2015	58.8±11.0 vs 58.6±9.8	2(7.1) vs 8(27.6)	NA	NA	0(0) vs 0(0)	0(0) vs 0(0)	28(100) vs 29(100)	NA
EUCLID	66.6±8.4 vs 66.5±8.5	1908(27.5) vs 1980(28.5)	76 (66-88) vs 77 (66-88)	NA	5651(81.5) vs 5659(81.4)	280(4.0) vs 289(4.2)	824(11.9) vs 810(11.6)	5406(78.0) vs 5413(77.8)
PHILO	67±12 vs 66±11	95(23.7) vs 93(23.3)	63 [35-104] vs 62 [36-109]	23.7 [15.6-43.4] vs 23.6 [14.2-38.6]	0 (0) vs 0 (0)	0(0) vs 0(0)	401(100) vs 400(100)	151(37.3) vs 157(39.3)
PLATO	62.1±11.2 vs 62.3±11.2	2655(28.4) vs 2633(28.3)	80 [28-174] vs 80 [29-180]	27 [13-68] vs 27 [13-70]	8566(91.8) vs 8511(91.6)	115(1.2) vs 114(1.2)	542(5.8) vs 554(6.0)	3360(36.0) vs 3318(35.7)
Steblovnik 2016	61±12 vs 64±9	3(15.0) vs 3(18.8)	NA	NA	NA	NA	NA	NA
TREAT	59.0 (51.6-65.2) vs 58.8 (51.6-65.5)	433(22.6) vs 437(23.2)	76.5 (68.0-88.0) vs 77.0 (67.0-87.0)	26.5 (24.0-29.8) vs 26.5 (24.0-29.4)	1100(57.5) vs 1077(57.1)	73(3.8) vs 61(3.2)	631(33.0) vs 639(33.9)	1276(66.7) vs 1229(65.2)

SD: standard deviation. BMI: Body mass index. IQR: inter-quartile range. NA: not available. Data given in n(%), or median (IQR), or median [range] or mean±SD unless otherwise specified.

Part B: comorbidities (ticagrelor arm vs. clopidogrel arm)

Study ID	Angina pectoris	Prior MI	Prior PCI	Prior CABG	PAD	Stroke	TIA
Angiolillo 2016	NA	9(17.8) vs 16(32.7)	19(37.3) vs 22(44.9)	5(9.8) vs 14(28.6)	1(2.0) vs 1(2.0)	0(0.0) vs 1(2.0) (ischemic)	0(0.0) vs 2(4.1)
Chen 2015	NA	NA	NA	NA	NA	NA	NA
EUCLID	NA	1242(17.9) vs 1280(18.4)	777(11.2) vs 733(10.5)		6930(100) vs 6955(100)	576(8.3) vs 567(8.2)	279(4.0) vs 228(3.3)
PHILO	25.4 vs 27.5	33(8.2) vs 31(7.8)	45(11.2) vs 42(10.5)	5(1.2) vs 1(0.3)	13(3.2) vs 14(3.5)	27(6.7) vs 28(7.0) (non-hemorrhagic)	6(1.5) vs 11(2.8)
PLATO	NA	1900(20.4) vs 1924(20.7)	1272(13.6) vs 1220(13.1)	532(5.7) vs 574(6.2)	566(6.1) vs 578(6.2)	353(3.8) vs 369(4.0) (non-hemorrhagic)	NA
Steblovnik 2016	NA	NA	NA	NA	NA	NA	NA
TREAT	NA	181(9.5) vs 152(8.1)	112(5.9) vs 99(5.2)	15(0.8) vs 13(0.7)	17(0.9) vs 16(0.8)	88(4.6) vs 89(4.7)	NA

MI: myocardial infarction. PCI: percutaneous coronary intervention. CABG: coronary artery bypass graft. SCAD: stable coronary artery disease. PAD: peripheral artery disease. TIA: transient ischemic attack. DM: diabetes mellitus. HF: heart failure. COPD: chronic obstructive pulmonary disease. NA: not available. Data given in n(%) unless otherwise specified)

Part C: comorbidities (continued) (ticagrelor arm vs. clopidogrel arm)

Study ID	DM	Hypertension	Dyslipidemia	Chronic renal disease	(Congestive) HF	COPD	Asthma	Gout
Angiolillo 2016	39.2 vs 32.7	86.3 vs 98.0	74.5 vs 85.7	13.7 vs 14.3	9.8 vs 4.1	NA	NA	NA
Chen 2015	NA	NA	NA	NA	NA	NA	NA	NA
EUCLID	2639(38.1) vs 2706(38.9)	5437(78.5) vs 5420(77.9)	5229(75.5) vs 5251(75.5)	NA	NA	NA	NA	NA
PHILO	154(38.4) vs 124(31.0)	305(76.1) vs 290(72.5)	314(78.3) vs 289(72.3)	18(4.5) vs 20(5.0)	30(7.5) vs 28(7.0)	7(1.7) vs 10(2.5)	12(3.0) vs 14(3.5)	23(5.7) vs 19(4.8)
PLATO	2326(24.9) vs 2336(25.1)	6139(65.8) vs 6044(65.1)	4347(46.6) vs 4342(46.7)	379(4.1) vs 406(4.4)	513(5.5) vs 537(5.8)	555(5.9) vs 530(5.7)	267(2.9) vs 265(2.9)	272(2.9) vs 262(2.8)
Steblovnik 2016	NA	NA	NA	NA	NA	NA	NA	NA
TREAT	336(17.6) vs 303(16.1)	1082(56.6) vs 1076(57.1)	533(27.9) vs 531(28.2)	NA	37(1.9) vs 36(1.9)	51(2.7) vs 45(2.4)	28(1.5) vs 45(2.4)	39(2.0) vs 32(1.7)

MI: myocardial infarction. PCI: percutaneous coronary intervention. CABG: coronary artery bypass graft. SCAD: stable coronary artery disease. PAD: peripheral artery disease. TIA: transient ischemic attack. DM: diabetes mellitus. HF: heart failure. COPD: chronic obstructive pulmonary disease. NA: not available. Data given in n(%) unless otherwise specified.

Part D: Baseline/pre-randomization non-study/concurrent medications (ticagrelor arm vs. clopidogrel arm)

Study ID	Aspirin	Clopidogrel	Statin	ACEI	ARB	Beta-blockers	Calcium-channel blockers	Nitrates	Diuretics
AFFECT EV	27(100) vs 28(100)	NA	27(100) vs 27(96)	25(93) vs 28(100)		25(93) vs 25(89)	NA	NA	NA
Angiolillo 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chen 2015	NA	NA	NA	NA	NA	NA	NA	NA	NA
EUCLID	4667(67.3) vs 4604(66.2)	2193(31.6) vs 2280(32.8)	5058(73.0) vs 5123(73.7)	2826(40.8) vs 2809(40.4)	1741(25.1) vs 1747(25.1)	NA	NA	NA	NA
PHILO	NA	NA	215(53.6) vs 205(51.3)	67(16.7) vs 64(16.0)	102(25.4) vs 95(23.8)	40(10.0) vs 44(11.0)	117(29.2) vs 109(27.3)	344(85.8) vs 353(88.3)	NA
PLATO	8827(94.6) vs 8725(94.2)	4293(46.0) vs 4282(46.1)	8373(89.7) vs 8289(89.2)	7090(76.0) vs 6986(75.2)	1143(12.2) vs 1125(12.1)	8339(89.3) vs 8336(89.7)	2769(29.7) vs 2789(30.0)	7181(76.9) vs 7088(76.3)	

Steblovnik 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA
TREAT	1890(98.8) vs 1865(98.9)	1898(100) vs 1876(100)	1781(93.1) vs 1763(93.5)	1157(60.5) vs 1137(60.3)	210(11.0) vs 182(9.7)	1444(75.5) vs 1431(75.9)	NA	1185(61.9) vs 1149(60.9)	NA

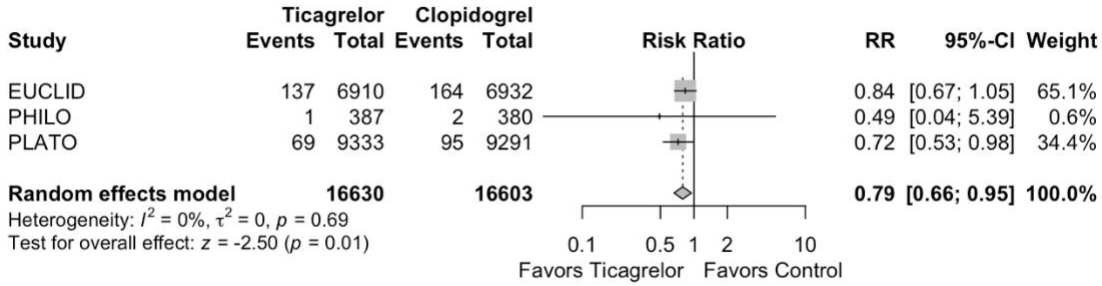
ACEI: angiotensin-converting-enzyme inhibitor. ARB: angiotensin-receptor blocker. NA: not available. Data given in n(%) unless otherwise specified.

Appendix 3: Results of quality assessment

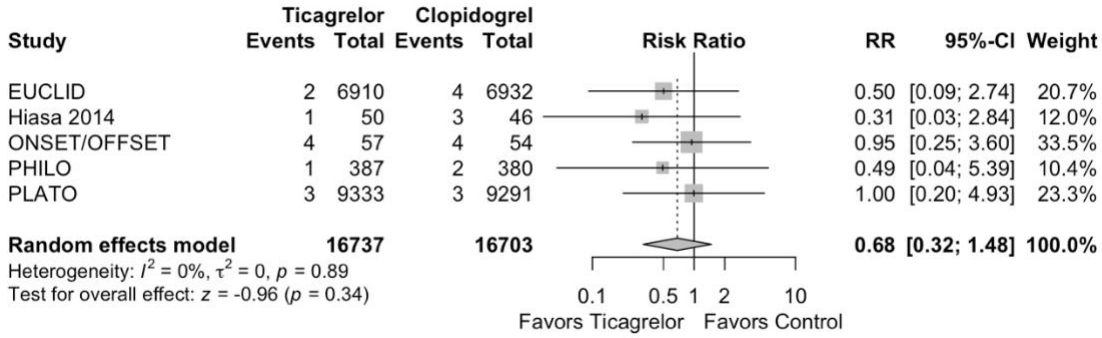
Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Others	Overall risk of bias
Angiolillo 2016	Low	Low	High	Low	Low	Low	Low	High
Chen 2015	Low	Low	High	Low	Low	Low	Low	High
EUCLID	Low	Low	Low	Low	Low	Low	Low	Low
PHILO	Low	Low	Low	Low	Low	Low	Low	Low
PLATO	Low	Low	Low	Low	Low	Low	Low	Low
Steblovnik 2016	Low	Low	High	Low	Low	Low	Low	High
TREAT	Low	Low	High	Low	Low	Low	Low	High

Appendix 4: Results of sensitivity analysis by excluding studies with high risk of bias

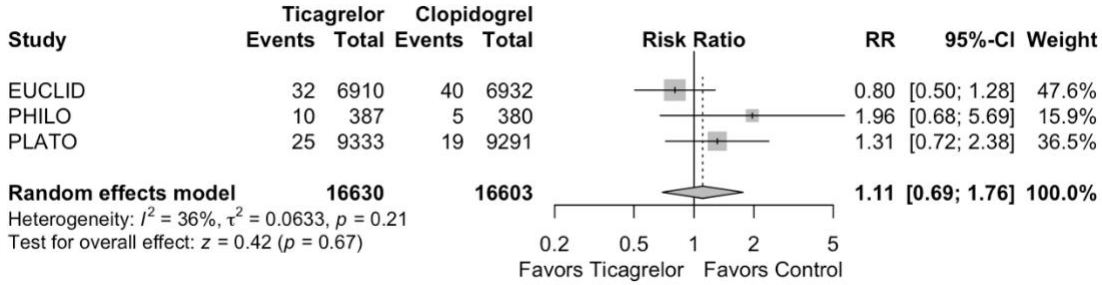
(A) Pneumonia



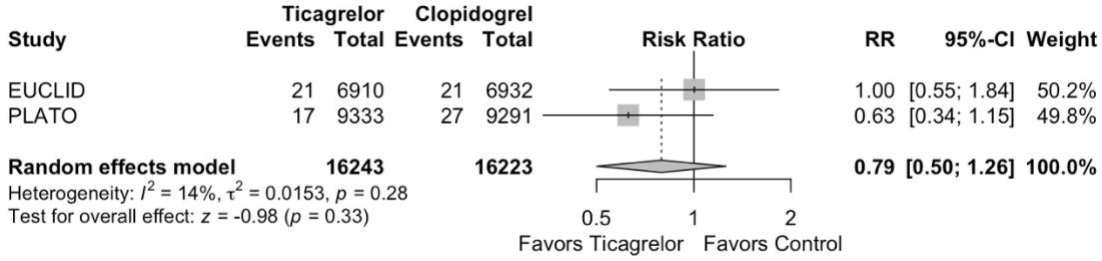
(B) URTI



(C) UTI

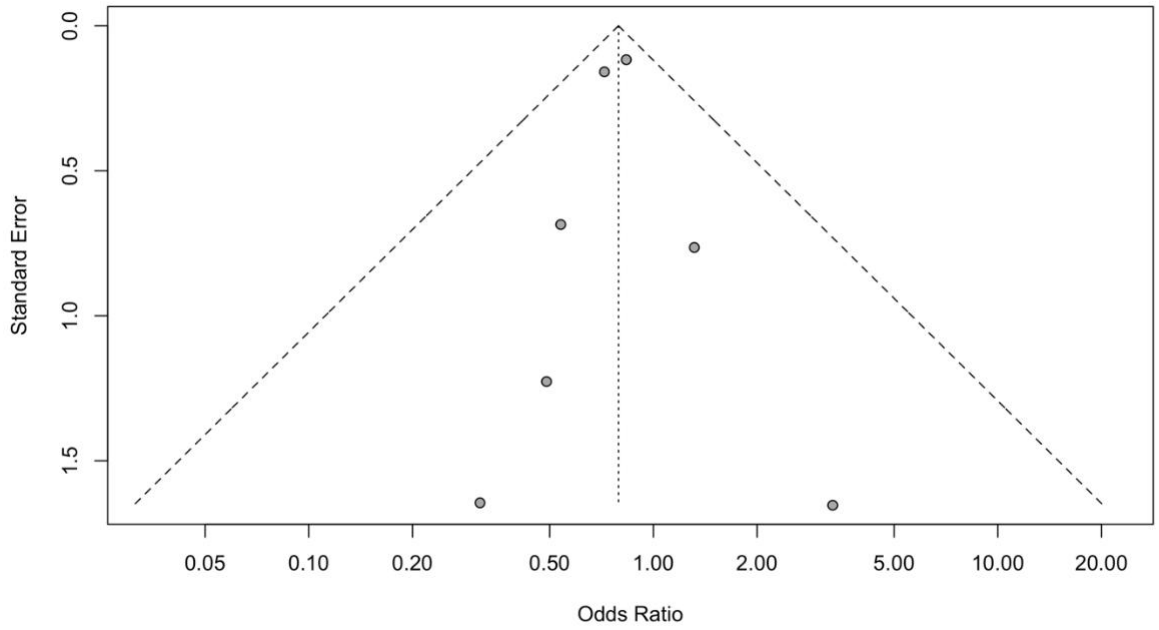


(D) Sepsis

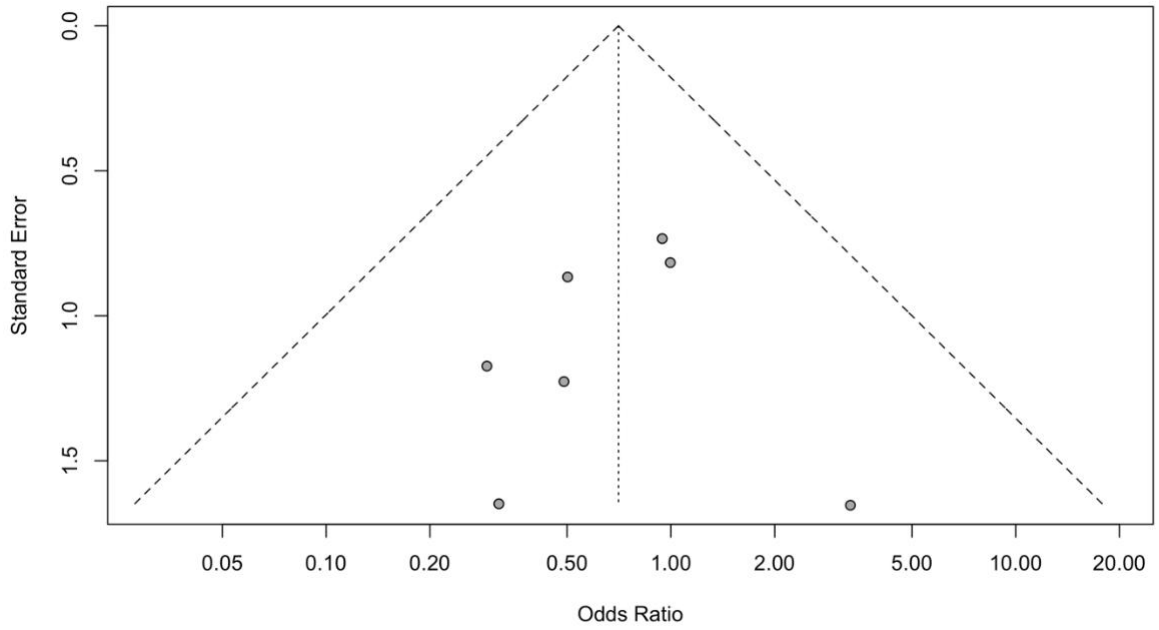


Appendix 5: Funnel plots

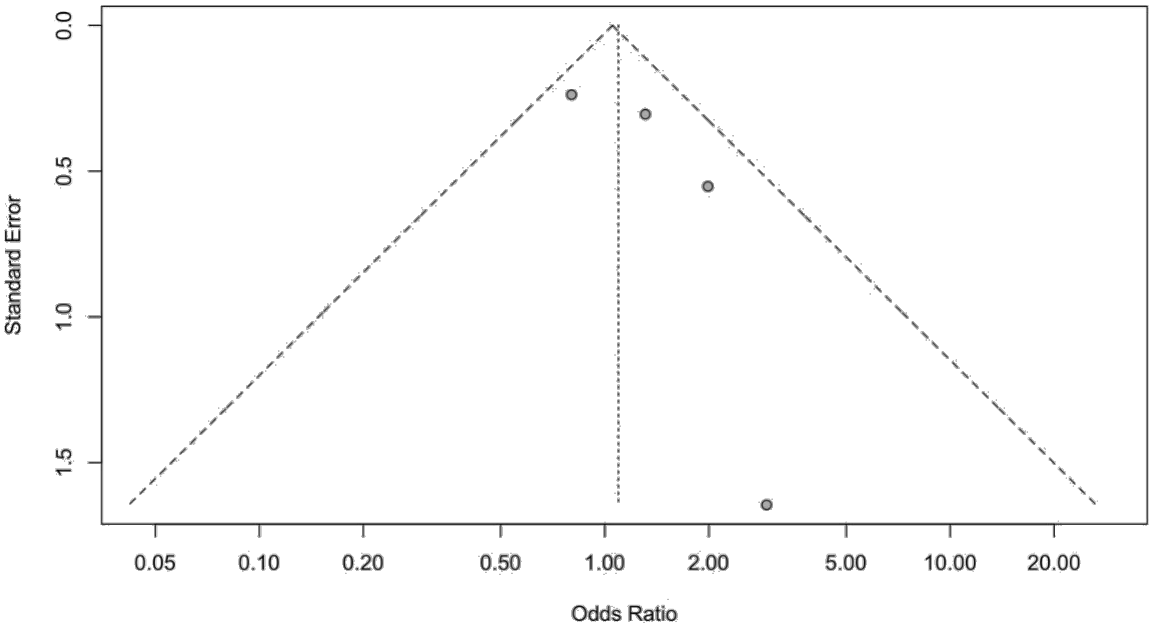
(A) Pneumonia



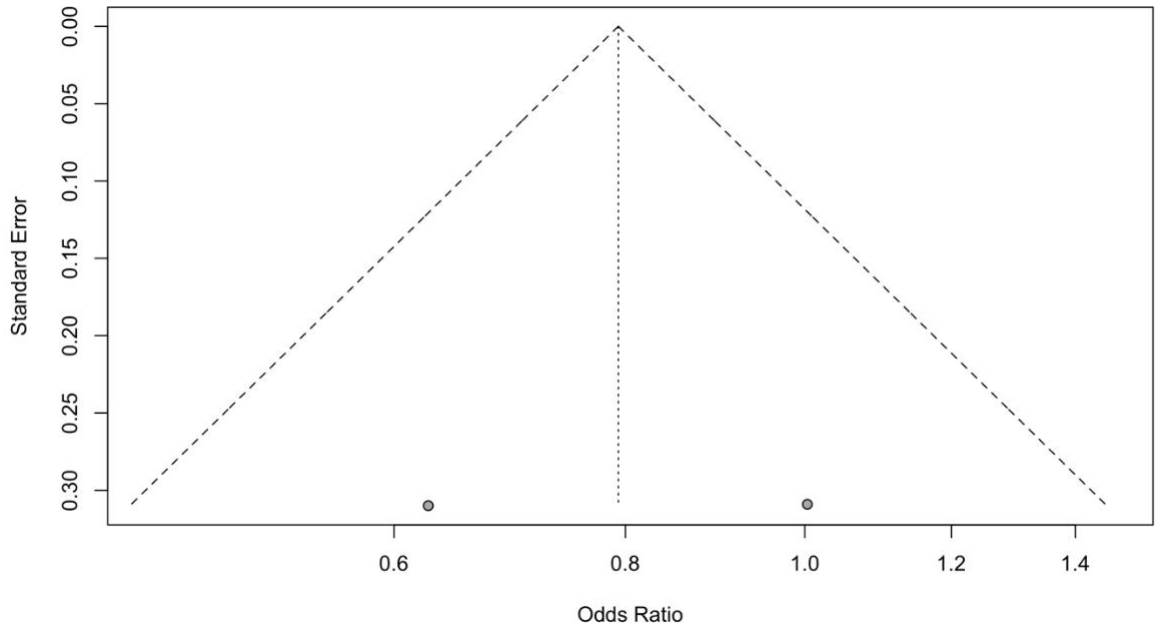
(B) URTI



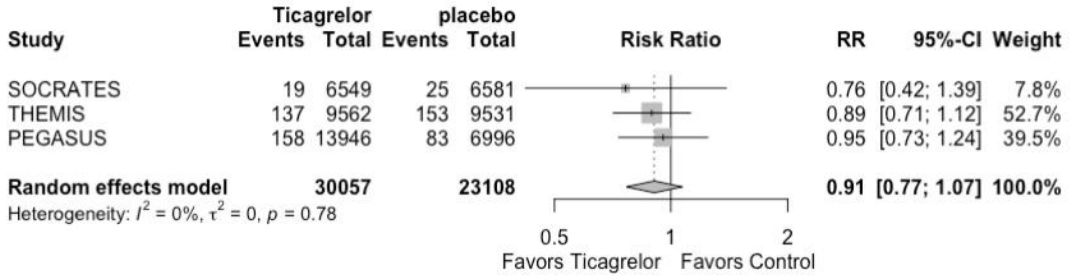
(C) UTI


Standard Error
0.0
0.5
1.0
1.5
0.05
0.10
0.20
0.50
1.00
2.00
5.00
10.00
20.00
Odds Ratio

(D) Sepsis


Standard Error
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.6
0.8
1.0
1.2
1.4
Odds Ratio

Appendix 6: Forest plot of the meta-analysis comparing ticagrelor versus placebo



References

1. Johnston SC, Amarenco P, Albers GW, et al. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med 2016;375:35–43. doi:10.1056/NEJMoa1603060
2. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309–20. doi:10.1056/NEJMoa1908077
3. Bonaca MP, Storey RF, Theroux P, et al. Efficacy and safety of ticagrelor over time in patients with prior MI in PEGASUS-TIMI 54. J Am Coll Cardiol 2017;70:1368–75. doi:10.1016/j.jacc.2017.07.768