Comparison of Clinical Outcomes Between Ticagrelor and Clopidogrel in Acute Coronary Syndrome: an Updated Meta-Analysis

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Research Article

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Abstract

Background: Ticagrelor is currently recommended for patients with acute coronary syndrome (ACS). However, recent studies have yielded controversial results.

Objective: To compare the clinical outcomes of ticagrelor and clopidogrel in ACS patients.

Methods: Three electronic databases were queried until April 1, 2021. Major adverse cardiovascular event (MACE) was the primary efficacy endpoint. The secondary efficacy endpoints included stroke, stent thrombosis (ST), cardiovascular (CV) death, all-cause death, and myocardial infarction (MI). The safety endpoints were (major and minor) bleeding. Odds ratios (ORs) and 95% confidence intervals (CIs) and were calculated to represent the estimated effect sizes.

Results: Nine clinical trials and 18 observational studies with 269,935 ACS patients were included. No significant difference was detected in MACE (OR 0.76, 95% CI 0.54-1.06, p = 0.11, I² = 66.74%), but ticagrelor introduced a higher risk of bleeding (1.49, 1.14-1.94, 0.00, 63.97%) and minor bleeding (1.57, 1.08-2.30, 0.02, 59.09%) in clinical trials. The secondary efficacy endpoints differed between clinical trials and observational studies. Subgroup analysis demonstrated that ticagrelor showed better therapeutic effects in patients underwent PCI (0.38, 0.23-0.63, 0.00, 0) than those intended for PCI (1.02, 0.70-1.49, 0.93, 68.99%). Meanwhile ticagrelor showed different therapeutic effects on ACS patients of different ethnicities and from different countries.

Conclusion:

This meta-analysis demonstrated that ticagrelor is not superior to clopidogrel in MACE but is associated with a higher risk of bleeding in ACS patients. Different PCI strategies, ethnicities, and countries may be the factors that contribute to different therapeutic efficacy of ticagrelor.

Introduction

Currently, cardiovascular disease (CVD) is the largest contributor to the disease burden, accounting for approximately one-third of the global deaths [1]. Besides, acute coronary syndrome (ACS) as a common and serious CVD, its incidence increases dramatically with age, proposing a great challenge to public medical care. Dual antiplatelet therapy (DAPT) is the mainstay treatment strategy against ACS, with timely vascularization as needed [2, 3]. As for the choice of antiplatelet agent, the 2016 American College of Cardiology (ACC) / American Heart Association (AHA) guidelines and the 2018 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend ticagrelor over clopidogrel for ACS treatment or the patients who have received percutaneous coronary intervention (PCI) [2, 4].

As a novel generated adenosine diphosphate receptor antagonist, ticagrelor provides faster, more potent, and more stable platelet inhibitory effects than clopidogrel [5, 6]. The large Platelet Inhibition and Patient Outcomes (PLATO) trial exhibited that compared with clopidogrel, ticagrelor reduced the incidence of stroke, myocardial infarction (MI), and cardiovascular (CV) death, without elevating the risk of major bleeding [7]. However, data from other large clinical trials [8, 9] and observational studies [10–12] drew controversial conclusions. Meanwhile, meta-analyses published recently also reported inconsistent results [13–16]. Therefore, we conducted a meta-analysis to review previous relevant studies and compare the clinical benefits of ticagrelor and clopidogrel treatments in the ACS population in the context of aspirin use to address these conflicting conclusions.

Methods

We reported the current meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [17] (Online Resource ESM_1), and have registered the study in an international prospective register of systematic reviews PROSPERO (ID: CRD42021251212).

Literature search

Three electronic databases, Cochrane, EMBASE, and PubMed library, were searched for eligible citations prior to April 1, 2021. The following relevant keywords were used: “ticagrelor”, “clopidogrel”, “myocardial ischemia”, “ACS”, “percutaneous coronary intervention”, and “PCI”. The detailed search strategy was summarized in Online Resource ESM_2. Additionally, reference lists in relevant meta-analyses were manually searched for potential eligibility.

Inclusion and exclusion criteria

We reviewed the full text of the potentially eligible literature to determine if they fulfilled the inclusion criteria as follows: (1) Adult (≥18 years old) patients with ACS who underwent PCI (PCI strategy proportion equal to 100%) or intended for PCI (proportion less than 100%); (2) Clinical trials and observational studies that compared ticagrelor versus clopidogrel in the context of aspirin use; (3) One or more of the following outcomes reported during any follow-up period: MACE, all-cause death, CV death, MI, stroke, stent thrombosis (ST), bleeding, major or minor bleeding. Literature that met the following exclusion criteria would be excluded: (1) Studies with incomplete data, or with only reported unadjusted endpoints in observational studies; (2) Studies from the same sample source; (3) Studies not in English.

Study end points

The primary efficacy endpoints were trial-defined primary MACEs or efficacy endpoints (described as death / CV death, MI, and / or stoke) (Online Resource ESM_3). The secondary endpoints included stroke, ST, MI, CV death, and all-cause death. The safety endpoints were trial-defined bleeding (a composite of major or minor bleeding), major bleeding, and minor bleeding (Online Resource ESM_3). For the definitions of safety outcomes, if not otherwise specified, we prioritized PLATO definitions when available.

Data extraction
Data from included citations were independently populated with a standardized data extraction by two researchers (SMY and CWC), with any discrepancy resolved by a third researcher (LLP). The data systematically extracted in this meta-analysis included the authors’ last names, study type, country (where the study was conducted), publication year and journal, disease subtype, sample size, age, the proportion of male and PCI strategy, dosing regimen, reported outcomes assessing efficacy and safety, and duration of follow-up.

**Quality assessment**

We assessed the risk of bias of randomized controlled trials (RCTs) using the Cochrane Risk Bias Assessment Tool, which covers six domains of bias, classified into three levels including “low bias”, “unclear”, and “high bias” [18]. Meanwhile, we assessed the quality of observational studies using the Newcastle-Ottawa Scale (NOS), which consists of eight items divided into three aspects including “selection”, “comparability”, and “outcome” assessment. The NOS adopts the semi-quantitative principle of star allocation to assess the literature quality, with a full score of nine stars [19].

**Statistical analysis**

We used the odds ratios (ORs) to represent the estimated effects, which along with the corresponding 95% confidence intervals (CIs) were obtained via the Stata 16.0 software (StataCorp, CollegeStation, TX, USA) [20]. Given the inclusion of heterogeneous populations, we chose the random-effects model to pool the effect sizes for this meta-analysis. Furthermore, we used the Higgins’ I² statistics and Cochran’s Q test to estimate heterogeneity across studies. A p value < 0.05 was considered as statistically significant.

All analyses were performed by analyzing data from clinical trials and observational studies separately to reduce the heterogeneity due to different study types. Meanwhile, subgroup analyses were performed to search for potential sources of heterogeneity. In brief, we performed two subgroup analyses, including propensity score-adjusted analyses (PA) group and multivariate-adjusted analyses (MA) group, in the observational studies according to different data types. Additionally, we conducted pre-specified subgroup analyses based on PCI strategy, ethnicity, country, and duration of follow-up in the included RCTs.

The stability of our findings was evaluated by sensitivity analysis, that is, calculating the effects by including high quality RCTs. When more than ten studies were included, the presence of publication bias was investigated by the Egger’s test and displayed by visual estimation (symmetry) of contour-enhanced funnel plots.

**Results**

**Eligible studies and patient characteristics**

The process of searching, retrieving, and screening in this meta-analysis is shown in Fig. 1. A total of 5,145 potentially relevant literatures were screened. Then 1,299 duplicates were excluded, and 3,767 were retrieved for title and abstract screening. Subsequently, the full texts of 79 articles were reviewed for eligibility. Among them, forty-two articles did not meet the inclusion criteria, eight presented with incomplete data, and two employed same cohorts included in our study. Finally, twenty-seven studies with 269,935 patients (87,988 and 181,947 in the ticagrelor and clopidogrel groups, respectively) were included for the meta-analysis. Nine studies were clinical trials [5, 7-9, 21-25], and 18 were observational studies [10-12, 26-40]. The patients were enrolled from 2003 to 2019, and the articles were published from 2007 to 2020. Among them, nineteen studies included ACS patients underwent PCI, and eight included those intended for PCI. 253,979 patients received PCI. The countries in which these studies were conducted were East Asian countries such as China, Korea, and Japan, as well as European and American countries such as the United States, Canada, Sweden, the Netherlands, and England. In addition, the ethnicities of the cohorts included both East Asians and Caucasians, and the duration of follow-up ranged from one month to 468 days. The main study and population characteristics are summarized in Table 1.

**Efficacy endpoints**

For the clinical trials, no significant difference was found in the primary efficacy endpoint (MACE) between ticagrelor and clopidogrel groups (OR 0.76, 95% CI 0.54-1.06, p = 0.11, I² = 66.74%; Fig. 2a). Similar results were shown in both the MA group (OR 0.97, 95% CI 0.82-1.15, p = 0.76, I² = 84.18%; Fig. 2b) and the PA group (OR 0.86, 95% CI 0.75-1.00, p = 0.05, I² = 72.32%; Fig. 2b) in observational studies.

The ticagrelor group demonstrated reduced secondary endpoints, compared to the clopidogrel group, regarding ST (OR 0.72, 95% CI 0.58-0.90, p = 0.00, I² = 0.00%; Table 2a) in clinical trials, all-cause death (OR 0.83, 95% CI 0.70-0.98 p = 0.03, I² = 69.89%) and CV death (OR 0.66, 95% CI 0.44-0.99, p = 0.04, I² = 70.59%) in the PA group, and CV death (OR 0.59, 95% CI 0.45-0.79, p = 0.001) in the MA group (Table 2b).

**Safety endpoints**

Ticagrelor led to significantly higher risks of bleeding (OR 1.49, 95% CI 1.14-1.94, p = 0.00, I² = 63.97%) and minor bleeding (OR 1.57, 95% CI 1.08-2.30, p = 0.02, I² = 59.09%) over clopidogrel in clinical trials (Table 2a). The increased risks of bleeding (OR 1.39, 95% CI 1.06-1.83, p = 0.02, I² = 76.11%) and minor bleeding (OR 1.61, 95% CI 1.37-1.89, p = 0.00, I² = 0.00%) were also identified in the PA group of observational studies (Table 2b). However, only the minor bleeding risk (OR 1.21, 95% CI 1.14-1.72, p = 0.007; Table 2b) increased significantly in the MA group of observational studies.

**Subgroup analysis**

In the subgroup of PCI strategy, patients underwent PCI (OR 0.38, 95% CI 0.23-0.63, p = 0.00, I² = 0) benefited more from ticagrelor than those intended for PCI (OR 1.02, 95% CI 0.70-1.49, p = 0.93, I² = 68.99%) in MACE (Fig. 3a), but ticagrelor introduced a higher risk of bleeding in the patients either underwent PCI
Subgroup analysis based on different ethnicity was performed to study the clinical outcomes of ticagrelor and clopidogrel between Caucasian and East Asian populations. Ticagrelor showed a superior MACE reducing effect over clopidogrel in Caucasian patients (OR 0.84, 95% CI 0.75-0.94, p = 0.00, I² = 0; Fig. 3b). Meanwhile, it was related to a lower risk of bleeding (OR 1.09, 95% CI 0.99-1.20, p = 0.07, I² = 0; Fig. 3b). However, the results were inconsistent in East Asian populations. Ticagrelor was comparable with clopidogrel regarding MACE (OR 0.67, 95% CI 0.36-1.25, p = 0.21, I² = 77.78%; Fig. 3b) and related to a higher bleeding risk (OR 1.81, 95% CI 1.43-2.29, p = 0.00, I² = 0; Fig. 3b).

Subgroup analysis based on different Asian countries showed that Chinese patients benefited more from ticagrelor treatment than those in Korean and Japanese, while the risk of bleeding significantly increased in all three Asian countries (Fig. 3c). Further subgroup analyses were conducted to analyze the safety and efficacy of ticagrelor in different follow-up duration classifications. It showed that bleeding risk and MACE was comparable between the two groups during the follow-up duration (Online Resource ESM_6).

**Sensitivity analyses and publication bias**

Sensitivity analyses were performed by including high quality RCTs. The results remained consistent, except for bleeding (OR 1.57, 95% CI 0.97-2.53, p = 0.06, I² = 84.86%; Online Resource ESM_8).

According to different data type, publication bias was investigated in the two groups: the composite of propensity score matched/adjusted studies and clinical trials, and the composite of multivariable adjusted studies and clinical trials. By contour-enhanced funnel plots (Fig. 4) and the results of the Egger's test (Table 3), we detected no publication bias except for MACE and MI in the composite of propensity score matched/adjusted studies and clinical trials. The results of nonparametric trim-and-fill analysis showed that five studies were filled for MACE with the total results influenced, and two were filled for MI with the total results unaffected (Online Resource ESM_9, Table 4).

**Discussion**

This meta-analysis, based on 27 studies, suggested that ticagrelor was not only inferior to clopidogrel in patients with ACS, but also related to an increased bleeding risk. Whereas, ticagrelor was more effective in the treatment of those who underwent PCI than clopidogrel, as it significantly reduced the incidence of MACE. Meanwhile the present meta-analysis revealed that Caucasians and East Asians had inconsistent safety and efficacy profiles under ticagrelor treatment. Among East Asian patients, Chinese benefited more from ticagrelor compared to Korean and Japanese. Care should therefore be taken to screen the eligible population when applying ticagrelor, and the bleeding risk under ticagrelor treatment was of concern.

Recently, several studies have revisited the issues concerning clinical applications of ticagrelor and clopidogrel. Wu et al. [13] found that ticagrelor treatment was more beneficial than clopidogrel treatment in European, American and Asian populations, who had a higher risk of bleeding. However, this analysis mixed all studies together and ignored the heterogeneity between clinical trials and observational studies. Furthermore, Guan et al. [15] reported that the efficacy endpoint of ticagrelor was comparable to that of clopidogrel, but the safety endpoint of ticagrelor should be further studied. Similarly, they performed a mixed analysis while including studies involving patients with stable coronary atherosclerotic heart disease (CAD). Consistently, Fan et al. [16] reported that ticagrelor only exhibited a tendency to reduce MACE at the expense of bleeding. Although the current meta-analysis differentiated RCTs and observational studies, no further subgroup analysis based on other study (or population) characteristics was performed. In this meta-analysis, we performed pre-specified subgroup analyses for MACE and bleeding according to PCI strategy, ethnicity, country, and follow-up duration in RCTs. Additionally, we performed two subgroup analyses (the PA and MA groups) in observational studies according to different data types. The aforementioned meta-analyses on this issue reported different clinical efficacy of ticagrelor, but they consistently found increased bleeding risk. We conducted a comprehensive analysis from both clinical trial and real-world practice considerations to compare the clinical outcomes of ticagrelor and clopidogrel in different subgroups of patients. Therefore, some definitive evidence can be provided for clinicians to choose from ticagrelor and clopidogrel.

We found similar primary efficacy results for ticagrelor treatment in both clinical trials and observational studies, though the MA group differed slightly. The secondary efficacy endpoints differed in clinical trials and observational studies, which can be attributed to inherent differences between study types. In brief, clinical trials (especially RCTs) match baseline characteristics well. And observational studies, although clinical factors associated with treatment selection can be matched by propensity score matched / adjusted analyses or multivariable adjusted analyses, there are still some unadjusted or incomplete adjustment variables that may affect the results. This may explain the difference in bleeding in MA group, as well as the difference in the secondary endpoints between clinical studies and observational studies.

In addition to pharmacological treatment with DAPT, the primary management of ACS patients involves an early invasive strategy consisting of coronary angiography, PCI, and even coronary artery bypass grafting (CABG) [2, 4, 41]. Considering that a high proportion of high-risk patients with ACS received PCI after coronary angiography, we included those who underwent or intended for PCI to better compare the clinical outcomes. Subgroup comparison in this study revealed that ticagrelor could significantly reduce the incidence of MACE in patients underwent PCI, but induced a higher bleeding risk than clopidogrel.

Whereas, in patients intended for PCI, ticagrelor was not superior over clopidogrel regarding MACE and bleeding. In ACS patients intended for PCI, the proportion of PCI strategy ranged from 42% (Cannon 2007) to 84.8% (Goto 2015) in the ticagrelor group in clinical trials, and from 88.5% (Sahlén 2016) to 92.3% (Vercellino 2017) in observational studies. Ahn et al. reported no significant difference in the outcomes between PCI and CABG complete revascularization [42]. Thus, ACS patients who received PCI and CABG had different clinical characteristics from those receiving medical treatment alone. Ticagrelor could significantly reduce the risk of MACE in patients undergoing PCI, providing valuable suggestions for clinicians to choose from ticagrelor and clopidogrel according to the PCI strategy.
In terms of ethnicity, Caucasians made up 91% of the population included in the PLATO trial, whereas East Asians accounted for only 6%. Caucasians and East Asians differ substantially in phenotypes and genomics; Caucasian based recommendations do not necessarily apply to East Asians [13]. We conducted subgroup analyses between different ethnicities, and we found that ticagrelor in Caucasian patients statistically decreased the incidence of MACE, while not increasing the risk of bleeding. However, this was not the case for East Asian populations, where ticagrelor had a comparable effect to clopidogrel on MACE but was more likely to cause bleeding events. East Asians are thought to be more prone to bleeding events than Caucasians, but are relatively resistant to adverse ischemic outcomes after PCI (the so-called “East Asian paradox”) [43–45]. In addition, cytochrome P450 2C19 loss-of-function alleles related to high platelet reactivity are more common in Asian populations [46]. In a nutshell, there are significant ethnic differences between Caucasian and East Asian patients in terms of thrombosis, platelet P2Y12 receptor inhibition, and predisposition to bleeding complications [43]. Those differences might partly contribute to this inter-population disparity. The number of RCTs included in this meta-analysis is relatively small, requiring more RCTs for further elaboration.

In East Asia, the MACE incidence was significantly reduced by ticagrelor in Chinese, but not in Korean and Japanese, which can, at least partially, be attributed to the different proportions of patients, underwent PCI. Specifically, The Korean TICAKOREA trial was a multicenter randomized study, in which 81.5% of the ACS patients assigned to the ticagrelor group underwent PCI [8]. In another PHILO trial conducted mainly in Japan, 84.8% of patients treated with ticagrelor received PCI [9]. More importantly, data from four Chinese trials showed that up to 94% of patients underwent PCI. The proportion of patients underwent PCI might be partly contributed to the efficacy difference of the ticagrelor treatment among Asian countries. Additionally, baseline characteristic of included population, diagnostic criteria, and dosage regimen might be the reasons for the differences. The efficacy of ticagrelor among Asian populations needs to be validated by larger trials.

DAPT reduces the incidence of thrombotic events but exposes patients to an increased risk of bleeding. The optimal DAPT duration subsequent to a PCI remains unclear. The safety and efficacy of short-duration (≤ 3 months) DAPT in elderly patients were acceptable [47], and abbreviated-duration (≤ 6 months) DAPT in CAD population did not significantly increase the incidence of MACE, but dramatically reduced the risk of major bleeding [48]. In addition, Verdia et al. reported that, compared to the standard one-year DAPT, a shorter-duration (3 or 6 months) could protect against major CV ischemic events in an improved manner [49]. In this meta-analysis, MACE and bleeding endpoints were comparable between 1-month and 6-month follow-up. The recommended DAPT duration has shifted from 12 months to a more flexible approach on the basis of the individual's ischemia and bleeding risk. Thus, balancing the risk of ischemia and bleeding when using DAPT becomes a clinical challenge because patients with a low risk of ischemic events and a high risk of bleeding would benefit from shorter duration[50].

The current study has several limitations. First, the sample sizes of several RCTs and the number of RCTs are relatively small. Due to limited research data or controversial results, the results of bleeding are not robust in sensitivity analyses. Second, the follow-up duration subsequent to PCI varied from in-hospital to one year or longer. Although we performed subgroup analysis in terms of the duration, the total results might also have swayed to some extent. Third, we pooled trials with heterogeneous populations that varied in study design, disease subtype, treatment strategy, and endpoints definitions. Fourth, possible adverse drug reactions, loss of tolerability, and discontinuation of treatment are not incorporated into the consideration.

Conclusion

We suggest that in ACS patients, ticagrelor is comparable in efficacy to clopidogrel, while it associates with a higher risk of bleeding. Clinicians should selectively adopt ticagrelor and clopidogrel according to different PCI strategy, ethnicities, and countries.

Declarations

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Author contribution

LLP contributed to the conception or design of the work. SMY, CWC and LLP contributed to the acquisition, analysis, or interpretation of data for the work. SMY and CWC drafted the manuscript. LLP critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflict of Interest

The authors declare no competing interests.

Ethical Approval

Not applicable.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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**Tables**

**Table 1** Main features of the included studies.
| No. | Study                                      | Study type | Country                               | Enrollment          | Population                                      | Ticagrelor group                                                                 | Clopidogrel group                                                                 |
|-----|--------------------------------------------|------------|---------------------------------------|---------------------|-------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1   | Yao, 2017/ Int J Clin Exp Med             | RCT        | China                                 | 2015.1-2016.6       | AMI patients undergoing PCI                      | 60 60.4 ± 12.7 63.3 100 Loading 180 mg; maintenance 90 mg once daily.          | 60 59.8 ± 10.8                                                                |
| 2   | Li, 2018/ Clinical cardiology             | RCT        | China                                 | 2014.1-2017.3       | STEMI patients undergoing PCI                    | 161 59.8 ± 11.2 83.6 100 Loading 180 mg; maintenance 90 mg twice daily.       | 281 62.8 ± 12.9                                                                |
| 3   | Tang, 2016/ J Cardiovasc Pharmacol        | RCT        | China                                 | 2013.1-2015.4       | ACS patients with or without ST elevation intending for invasive management | 200 64.36 ± 11.41 71 100 Loading 180 mg; maintenance 90 mg twice daily.       | 200 64.18 ± 11.09                                                              |
| 4   | Park, 2019/ Circulation                   | RCT        | Korea                                 | 2014.7-2017.6       | ACS patients with or without ST elevation intending for invasive management | 400 62.5 ± 11.3 74.2 81.5 Loading 180 mg; maintenance 90 mg twice daily.       | 400 62.3 ± 11.5                                                                |
| 5   | Goto, 2015/ Circulation Journal           | RCT        | Japan, Taiwan and South Korea        | NA                  | ACS patients with or without ST elevation intending for invasive management | 401 67 ± 12.0 76.3 84.8 Loading 180 mg; maintenance 90 mg twice daily.       | 400 66 ± 11                                                                   |
| 6   | Cannon, 2010/ Lancet                      | RCT        | 43 countries                          | NA                  | ACS patients intending for invasive management   | 6732 61.0 (53-69) # 74.8 76.6 Loading 180 mg; maintenance 90 mg twice daily.   | 6676 61.0 (53-70) #                                                                |
| 7   | Wang, 2016/ Therapeutics and Clinical Risk Management | RCT        | China                                 | 2013.8-2014.9       | ACS patients (65-93 years) intending for invasive management | 100 79 (76-85) # 69 75 Loading 180 mg; maintenance 90 mg twice daily.       | 100 80 (74-86) #                                                                |
| 8   | Cannon, 2007/ JACC                        | RCT        | 14 countries                         | 2004.10-2005.8      | NSTE-ACS patients intending for invasive management | 334 64 ± 12.1 61 42 Loading 270 mg; maintenance 90 mg twice daily.         | 327 62 ± 11.0                                                                  |
| 9   | Ren, 2015/ Herz                           | Non RCT    | China                                 | NA                  | NSTEM patients undergoing PCI                    | 149 56 ± 9.2 68.3 100 Loading 180 mg; maintenance 90 mg twice daily.         | 151 55 ± 8.0                                                                   |
| 10  | *Turgeon, 2020/ JAMA Internal Medicine    | Cohort     | Canada                                | 2012.4-2016.3       | ACS patients undergoing PCI                      | 3711 61 (54-69) # 76.9 100 NA                                               | 3711 61 (55-71) #                                                                |
| 11  | *You, 2020/ JAMA                          | Cohort     | America, South Korean                 | 2011.9-2019.3       | ACS patients undergoing PCI                      | 31290 NA 70.6 100 NA                                                       | 31290 NA                                                                       |
| 12  | Yudi, 2016/ Internal Medicine Journal     | Cohort     | Australia                             | 2009.7-2013.11      | STEMI and NSTEACS patients undergoing PCI        | 526 61.7 ± 11.8 78.1 100 NA                                                 | 956 67.5 ± 12.8                                                                |
| 13  | *Wang, 2018/ Chinese, Medical Journal     | Cohort     | China                                 | 2011.10-2014.8      | ACS patients undergoing PCI                      | 779 60.54 ± 10.53 71.1 100 NA                                               | 1558 60.97 ± 10.54                                                             |
| 14  | Sahle’n, 2016/ European Heart Journal     | Cohort     | Sweden                                | 2010.1-2013.12      | AMI patients intending for PCI                   | 11954 67 (59-75) # 71.5 88.5 NA                                             | 33119 71 (62-80) #                                                               |
| 15  | *Sun, 2019/ Atherosclerosis               | Cohort     | China                                 | 2014.8-2017.10      | ACS patients undergoing PCI                      | 1833 59.86 ± 10.12 74.9 100 NA                                               | 1833 60.35 ± 10.62                                                              |
|   | Study Details | Cohort/ Country | Study Period | Population | Age (Mean ± SE) | Male (%) | Loading | Maintenance | Comparison | Notes |
|---|--------------|-----------------|--------------|------------|-----------------|---------|---------|-------------|------------|-------|
| 16 | Völz, 2020/J Am Heart Assoc | Cohort Sweden | 2005.1-2015.1 | ACS patients undergoing PCI | 2929 | 67.25 ± 11.64 | 72.7 | 100 | NA | 12168 | 67.30 ± 11.48 |
| 17 | * Peyracchia, 2019/American Journal of Cardiovascular Drugs | Cohort Countries of America, Asia and Europe | 2003-2016 | ACS patients undergoing PCI | 798 | 60.19 @ | 82.7 | 100 | NA | 1831 | 60.51 |
| 18 | * Park, 2016/International Journal of Cardiology | Cohort Korea | 2011.11-2015.6 | AMI patients undergoing PCI | 1377 | 63 (53-72) @ | 74.2 | 100 | Loading 180 mg; maintenance 90 mg twice daily | 1377 | 62.24 ± 12.53 |
| 19 | Olier, 2018/Heart (British cardiac society) | Cohort England and Wales | 2007.1-2014.12 | STEMI patients undergoing PCI | 13 105 | 63 (53-72) @ | 74.2 | 100 | NA | 58 248 | 64 (54-75) @ |
| 20 | Krishnamurthy, 2019/Interventional cardiology | Cohort UK | 2009.1-2011.12 | STEMI patients undergoing PCI | 811 | 63 (19) $ | 72.4 | 100 | NA | 1648 | 65 (21) $ |
| 21 | Kim, 2019/Journal of Cardiology | Cohort Korea | 2013-2014 | AMI patients undergoing PCI | 4811 | 57 (50-65) @ | 86 | 100 | Loading 180 mg; maintenance 90 mg twice daily | 15459 | 60 (52-68) @ |
| 22 | * Choe, 2019/International Journal of Cardiology | Cohort Korea | 2011.11-2015.6 | ACS patients undergoing PCI | 1203 | 66 (56-74) @ | 71.7 | 100 | Loading 180 mg; maintenance 90 mg twice daily | 1203 | 67 (56-75) @ |
| 23 | * Chen, 2016/Journal of the Chinese Medical Association | Cohort Taiwan | 2013.7-2015.2 | ACS patients intending for PCI | 224 | 63.8 ± 13.3 | 79.9 | 87.1 | NA | 224 | 63.7 ± 13.7 |
| 24 | Zocca, 2017/EuroIntervention | Cohort Netherlands | 2012.12-2015.8 | ACS patients undergoing PCI | 1053 | 63.9 ± 12.1 | 71 | 100 | Loading 180 mg; maintenance 90 mg twice daily | 1009 | 62.9 ± 11.6 |
| 25 | Alexopoulos, 2016/Journal of Thrombosis and Haemostasis | Cohort Greece | 2012.1-2013.8 | ACS patients undergoing PCI | 717 | 60.1 ± 11.4 | 84.9 | 100 | Maintenance 90 mg twice daily | 959 | 65.3 ± 12.5 |
| 26 | Welsh, 2019/Canadian Journal of Cardiology | Cohort 20 countries | 2010.8-2014.7 | STEMI patients undergoing PCI | 2188 | NA | 77.9 | 100 | NA | 6500 | NA |
| 27 | Vercellino, 2017/BMC Cardiovascular Disorders | Case-control Italy | 2011.2-2013.6 | STEMI patients intending for PCI | 142 | 66 (56-73) @ | 73.9 | 92.3 | NA | 259 | 67 (56-67) @ |

**Note:** *Subset following propensity-score matching; @recorded as median (Q1-Q3); $recorded as median; $recorded as median (IQR); the rest data of age recorded as mean ± standard error.*

**Abbreviations:** ACS, acute coronary syndrome; AMI, acute myocardial infarction; NSTE-ACS, non-ST-elevation ACS; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; Non RCT, non-randomized controlled trial; NA, not available.

**Table 2** Comparison of ticagrelor and clopidogrel treatment for the safety and secondary efficacy endpoints in clinical trials and observational studies.

a. Comparison in clinical trials
### Outcomes

| Outcomes              | Trials | OR (95%CI)          | I²     | P Value |
|-----------------------|--------|---------------------|--------|---------|
| Bleeding              | 7      | 1.49 (1.14, 1.94)   | 63.97  | 0.00 *  |
| Major bleeding        | 6      | 1.22 (0.86, 1.73)   | 49.83  | 0.27    |
| Minor bleeding        | 6      | 1.57 (1.08, 2.30)   | 59.09  | 0.02 *  |
| All-cause death       | 7      | 0.88 (0.66, 1.17)   | 16.17  | 0.37    |
| CV death              | 7      | 0.90 (0.59, 1.36)   | 40.73  | 0.61    |
| MI                    | 7      | 0.84 (0.59, 1.21)   | 44.50  | 0.35    |
| Stoke                 | 7      | 1.04 (0.78, 1.38)   | 0      | 0.81    |
| Stent thrombosis      | 3      | 0.72 (0.58, 0.90)   | 0      | 0.00 *  |

**Note:** *significant p-value compared with clopidogrel group.

**Abbreviations:** CV death, cardiovascular death; MI, myocardial infarction; CI, confidence intervals; OR, odds ratios.

### b. Comparison in observational studies

| Outcomes              | Propensity score-matched/adjusted analyses | Multivariable-adjusted analyses |
|-----------------------|-------------------------------------------|---------------------------------|
|                       | NO. | OR (95%CI) | I² | P Value | NO. | OR (95%CI) | I² | P Value |
| Bleeding              | 7   | 1.39 (1.06, 1.83) | 76.11 | 0.02 * | 6   | 1.15 (0.86, 1.53) | 81.88 | 0.35 |
| Major bleeding        | 8   | 1.26 (0.90, 1.75) | 75.23 | 0.17 | 2   | 1.12 (0.86, 1.45) | 0 | 0.39 |
| Minor bleeding        | 4   | 1.61 (1.37, 1.89) | 0.00 | 0.00 * | 1   | 1.21 (1.14, 1.72) | - | 0.007 * |
| All-cause death       | 13  | 0.83 (0.70, 0.98) | 69.89 | 0.03 * | 8   | 0.90 (0.75, 1.07) | 79.34 | 0.23 |
| CV death              | 6   | 0.66 (0.44, 0.99) | 70.59 | 0.04 * | 1   | 0.59 (0.45, 0.79) | - | <0.001 * |
| MI                    | 11  | 0.99 (0.84, 1.15) | 48.41 | 0.87 | 4   | 0.9 (0.71, 1.15) | 79.13 | 0.39 |
| Stoke                 | 11  | 0.84 (0.65, 1.09) | 39.97 | 0.19 | 4   | 0.79 (0.59, 1.06) | 52.70 | 0.12 |
| Stent thrombosis      | 5   | 1.18 (0.81, 1.72) | 6.26 | 0.39 | 2   | 1.45 (0.89, 2.37) | 0 | 0.14 |

**Note:** *significant p-value compared with clopidogrel group.

**Abbreviations:** CV death, cardiovascular death; MI, myocardial infarction; CI, confidence intervals; OR, odds ratios.

### Table 3 Publication bias of outcomes using Egger test.

| Outcomes              | Propensity score-matched/adjusted studies and clinical trials | Multivariable-adjusted studies and clinical trials |
|-----------------------|-------------------------------------------------------------|---------------------------------------------------|
|                       | Studies | Prob > | z | Studies | Prob > | z |
| MACE                  | 22      | 0.0184 | 15 | 0.1035 |
| All-cause death       | 20      | 0.9928 | 15 | 0.729  |
| CV death              | 13      | 0.7681 | 8  | NA     |
| MI                    | 18      | 0.0464 | 11 | 0.107  |
| Stoke                 | 18      | 0.5027 | 11 | 0.9779 |
| Stent thrombosis      | 9       | NA     | 5  | NA     |

**Note:** Publication bias was detected when the number of studies ≥ 10; P > 0.05, no significant publication bias.

**Abbreviations:** MACE, major adverse cardiac events; CV death, cardiovascular death; MI, myocardial infarction; NA, not available.

### Table 4 Nonparametric trim-and-fill analysis.
| Outcomes | Studies                  | Number | LnOR   | 95% CI     |
|----------|--------------------------|--------|--------|------------|
| MACE     | observed                 | 22     | -0.169 | -0.299, -0.039 |
|          | observed + imputed       | 22+5   | -0.072 | -0.205, 0.062 |
| MI       | observed                 | 19     | -0.005 | -0.058, 0.049 |
|          | observed + imputed       | 19+2   | -0.001 | -0.054, 0.053 |

**Abbreviations**: MACE, major adverse cardiac events; MI, myocardial infarction; CI, confidence intervals; OR, odds ratios.

**Figures**

Potentially relevant papers identified $n = 5145$
- EMBASE $n = 3492$
- PubMed $n = 960$
- Cochrane $n = 691$
- Additional records identified through other sources $n = 2$

Duplicates excluded $n = 1299$

Titles and abstracts screened for retrieval $n = 3846$

Studies excluded $n = 3767$

Potentially appropriate studies to be included in systematic review $n = 79$

Studies excluded $n = 50$
  - With incomplete data $n = 8$
  - Did not fulfill inclusion criteria $n = 42$

Studies included in systematic review $n = 29$

Studies excluded from meta-analysis $n = 2$
  - Data from same sample origin $n = 2$

Studies included in meta-analysis $n = 27$

**Figure 1**

Flowchart diagram of searching and screening of studies.
Figure 2

Comparison the primary efficacy outcomes (MACE) between ticagrelor and clopidogrel treatment. Forest plots reporting outcomes in clinical trials (a) and observational studies (b). MACE, major adverse cardiac events.
Figure 3

Subgroup comparison of MACE and bleeding outcomes between ticagrelor and clopidogrel treatment according to PCI strategy (a), ethnicity (b), Asian countries (c) in RCTs. MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.
Figure 4

Publication bias of outcomes using Contour-enhanced funnel plots. (a) Publication bias of outcomes in propensity score matched/adjusted studies and clinical trials; (b) Publication bias of outcomes in multivariable adjusted studies and clinical trials. MACE, major adverse cardiovascular events; CV death, cardiovascular death; MI, myocardial infarction.

Supplementary Files

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