RESEARCH ARTICLE

The clinical efficacy and safety evaluation of ticagrelor for acute coronary syndrome in general ACS patients and diabetic patients: A systematic review and meta-analysis

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Abstract

Objective

In this study, a systematic evaluation was conducted to estimate the efficacy and safety of ticagrelor for treating acute coronary syndrome (ACS) in general ACS patients and a diabetes mellitus (DM) group.

Methods

A search of PubMed, Cochrane Central Register of Controlled Trials, Web of Science, CNKI databases was conducted to analyze relevant randomized controlled trials (RCTs) of ticagrelor treating ACS during 2007 to 2015. Article screening, quality accessing and data extracting was independently undertaken by two reviewers. A meta-analysis was performed to clarify the efficacy and safety of ticagrelor in general ACS patients, and a meta-regression analysis was taken to demonstrate the efficacy and safety of ticagrelor in DM patients compared with general ACS patients.

Result

Twenty-two studies with 35004 participants were included. The meta-analysis result implied that ticagrelor could: 1) reduce the incidence of the composite endpoint [OR = 0.83, 95%CI (0.77, 0.90), P <0.00001] and the incidence of myocardial infarction [OR = 0.81, 95%CI (0.74, 0.89), P = 0.0001]; 2) not statistically reduce the incidence of cardiovascular death, the platelet reactivity of patients 6 hours or 8 hours after administration, or the incidence of bleeding events; 3) increase the incidence of dyspnea [OR = 1.90, 95%CI (1.73, 2.08), P <0.00001] compared with clopidogrel. Meanwhile, compared with prasugrel, ticagrelor could 1) reduce the platelet reactivity of patients at maintenance dose [MD = -44.59, 95%CI (-59.16, -30.02), P <0.00001]; 2) not statistically reduce the incidence of cardiovascular death, the platelet reactivity of patients 6 hours or 8 hours after administration, or the incidence of bleeding events; 3) induce the incidence of
Introduction

Acute coronary syndrome (ACS) refers to a group of clinical conditions such as coronary atherosclerosis rupture, platelet aggregation and thrombosis. Platelet aggregation has a close relationship with the occurrence and development of ACS; thus, antiplatelet therapy is the most common treatment for ACS.

Second-generation thienopyridines (clopidogrel and prasugrel) are widely used in antiplatelet therapy. Clopidogrel is converted to its active metabolites in vivo by a 2-step process, and these active metabolites irreversibly inhibit the platelet P2Y12 adenosine diphosphate receptor [1, 2]. Therefore, clopidogrel is a prodrug, and its onset of action is relatively slow [3]. Moreover, 30% of patients show drug resistance to clopidogrel, which can induce a high risk of myocardial infarction recurrence and stent thrombosis [4]. Prasugrel is another antiplatelet drug with the same mechanism as clopidogrel. Its active metabolites are produced in a 1-step metabolic process; thus, its onset of action is shorter [5]. Furthermore, compared with clopidogrel, it has a series of advantages, such as greater efficacy and lower variability. However, it probably has an increased risk of bleeding, including fatal bleeding [6–8]. Given the limitations of these two widely used drugs, such as the delayed onset of action and variability of clopidogrel and prasugrel bleeding risk, additional studies were critical in developing efficient new P2Y12 receptor antagonists.

Ticagrelor (AZD6140) is the first reversibly binding oral P2Y12 receptor antagonist that blocks ADP-induced platelet aggregation. The discovery of ticagrelor began with adenosine triphosphate (ATP). The subsequent identification of a novel series of P2Y12 receptor antagonists and the exploitation of their SAR has been described. Modifications of the acidic side chain and purine core, in addition to experimentation with hydrophobic substituents, led to the development of a series of neutral molecules. Ultimately, the leading compound, AZD6140, was developed as a novel platelet aggregation inhibitor [9].

Unlike the thienopyridines, ticagrelor is not a prodrug and therefore does not require metabolic activation. It binds reversibly to the receptor and exhibits rapid onset and offset of action, which closely follows drug exposure levels [10]. The action mechanism of ticagrelor facilitates the rapid recovery of platelet function after drug withdrawal. Ticagrelor also has a stronger and more consistent effect than clopidogrel because its direct action does not require catabolite activation [11].

Several clinical studies have indicated that ticagrelor is superior to clopidogrel in reducing platelet reactivity, myocardial infarction, cardiovascular death, stroke and adverse events [12].

Conclusion

Ticagrelor could reduce the incidence of composite endpoint of cardiovascular death, myocardial infarction and stroke as well as platelet reactivity in DM patients with ACS, while not increasing the risk of bleeding. Because there are differences in platelet reactivity between DM patients and general ACS patients, we suggest that caution is needed when using ticagrelor in clinical applications.
It may also reduce the incidence of clinical bleeding events compared with prasugrel [13, 14]. However, some authors have noted that the bleeding risk of the two treatments is not significantly different [15]. Therefore, further research is needed to estimate the safety of ticagrelor compared to the other two drugs.

During our analysis of clinical studies on ticagrelor, clopidogrel and prasugrel, we found that a significant proportion of patients with ACS have comorbid diabetes mellitus (DM). This result underscores the fact that DM is an important risk factor for ACS. DM enhances the risk of coronary and cerebrovascular diseases [16] and significantly increases the risk of major cardiovascular complications [17, 18]. Diabetic patients comprise a unique subpopulation within ACS, and the clinical effects of aspirin are different in diabetic patients than in other ACS patients. According to a meta-analysis by De Berardis G et al., the benefit of aspirin in DM patients is well below expectations, which may be explained by the rapid recovery of platelet reactivity in DM patients [19]. Although some clinical studies have started to focus on the clinical efficacy of ticagrelor in DM patients, a systematic review of the efficacy and safety of ticagrelor in DM patients with ACS has been lacking.

Therefore, in this article, we systematically evaluated the efficacy and safety of ticagrelor in DM patients with ACS compared with clopidogrel and prasugrel. The results may provide a guideline for more effective treatment of ACS in patients with DM.

**Materials and methods**

**Search strategy and eligibility criteria for study selection**

Randomized controlled trials comparing the clinical efficacy of ticagrelor and clopidogrel or prasugrel in treating ACS, published from 2007 to 2015, were screened for inclusion in this study. The PubMed, Cochrane Central Register of Controlled Trials, Web of Science, China National Knowledge Infrastructure (CNKI) databases were searched using the following terms: "ticagrelor or AZD6140 or Brilinta" and "clopidogrel or Plavix or prasugrel or CS-747 or LY 640315" and “acute coronary syndrome or stable coronary artery” and “randomized controlled trails”. The detailed search strategy was provided in S1 Fig.

Reviews and other relevant articles were also searched to identify all potential results. The citation lists of the retrieved articles were manually screened by the inclusion and exclusion criteria. The detail of inclusion criteria were as follows: 1) study designs were clearly described as clinical trials; 2) Ticagrelor was used as the experimental drug, and either clopidogrel or prasugrel was used as the positive control drug; 3) patients in the ticagrelor group were given a loading dose of 180 mg orally, followed by a maintenance dose of 90 mg twice a day; patients in the clopidogrel group were given a loading dose of 300 mg orally followed by a maintenance dose of 75mg; patients in the prasugrel group were given a loading dose of 60 mg orally, followed by a maintenance dose of 10 mg twice a day; and all patients were given aspirin 75–100 mg per day unless they were intolerant; 4) the duration of treatment was less than 12 months; and 5) participants were suffering from ACS with unstable angina, non-ST segment elevation myocardial infarction or ST segment elevation myocardial infarction. In addition, exclusion criteria were as follows: 1) original studies were non-clinical trials; 2) the drug in the control group was neither clopidogrel nor prasugrel; 3) endpoints in the studies were not in accordance with the endpoints in this systematic review; 4) studies had insufficient data for analysis; and 5) the article is a review or letter.

**Endpoints of evaluation**

The primary endpoint is a composite endpoint (containing the probability of any myocardial infarction, cardiovascular death or stroke). Secondary endpoints included the incidence of
myocardial infarction (MI), cardiovascular death (CVD), stroke and the platelet reactivity. The endpoints in the safety evaluation included bleeding events and dyspnea.

Data extraction

Two investigators (QT and SX) independently screened the articles and extracted the data from the included studies using standard data-abstraction forms. Disagreements were resolved by discussion with another reviewer (JX). Extracted data were transferred to Review Manager 5.2 for meta-analysis and Stata 12.0 for meta-regression analysis.

The following information was extracted from included studies: First author, year of publication, disease that participants suffered, intervention, efficacy outcomes and adverse events.

Risk of bias analysis

Two reviewers (QT and SX) independently assessed the quality of the included studies according to the Cochrane risk of bias tool, which assesses the following six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias [20].

Statistical methods

The meta-analysis was prepared using Review Manager 5.2 software. The data extracted from the included studies were used to calculate odds ratios (OR), mean difference (MD) and 95% confidence intervals (CIs). A fixed-effects model was applied to the overall analysis and subgroup analysis if no heterogeneity was expected while a random-effects model was applied if heterogeneity was present. \( I^2 (>50\%) \) calculated by Review Manager 5.2 software were taken as the determinant of heterogeneity and \( P ( <0.05) \) was considered statistically significant. Publication bias was assessed with Harbord’s test (for dichotomous variables) or Egger’s test (for continuous variables), significant publication bias was indicated when \( P <0.05 \). These data were depicted in funnel plots.

The meta-regression analysis, prepared using Stata 12.0 software, was used to evaluate the relationship between the DM patient proportion and the efficacy and safety endpoints.

Result

Description of the studies

A detailed description of study screening is illustrated in Fig 1. A total of 596 studies were identified through database searches; 77 additional records were identified through other sources. After removing any duplicates, 615 studies remained. Among them, 489 studies were excluded by screening of title and abstract, 102 studies were excluded for lack of analyzed outcomes, and 2 studies were excluded for insufficient data for analysis. Twenty-two studies [1, 21–41] covering a total of 35,004 participants were finally included in this systematic review.

The basic characteristics of the included studies are listed in Table 1. The analysis included patients with acute coronary syndrome, such as coronary artery disease (CAD), non-ST segment elevation myocardial infarction (NSTEMI), ST segment elevation myocardial infarction (STEMI) and unstable angina. Among the 22 included studies, 14 studies compared the clinical efficacy of ticagrelor and clopidogrel, while 8 studies compared ticagrelor to prasugrel. The outcomes evaluated between ticagrelor groups and clopidogrel or prasugrel groups varied across the included studies. Pooled outcomes contained incidence of the composite endpoint, platelet reactivity, the incidence of bleeding events, the incidence of myocardial infarction, the incidence of cardiovascular death, the incidence of stroke and the incidence of dyspnea.

The Cochrane risk of bias tool was used to measure the quality of the included studies, and the results are shown in Figs 2 and 3. Most of the included studies describe the detail of
Table 1. Characteristics of included studies.

| No. | Year | Patients (DM Patients) | Disease | Intervention | Outcomes a |
|-----|------|-------------------------|---------|--------------|------------|
| 1   | [21] | 2010 13408 (3109)       | ACS     | Ticagrelor vs Clopidogrel | 1, 3, 4, 5, 6 |
| 2   | [22] | 2013 100 (100)          | ACS     | Ticagrelor vs Prasugrel   | 2, 3, 5     |
| 3   | [23] | 2014 405 (108)          | ACS with CABG | Ticagrelor vs Clopidogrel | 1, 3     |
| 4   | [1]  | 2013 30 (30)            | ACS with DM | T-P vs P-T       | 2, 3, 4, 7  |
| 5   | [24] | 2014 58 (32)            | CAD with DM | Ticagrelor vs Clopidogrel | 2       |
| 6   | [25] | 2014 60 (23)            | APC in ACS | Ticagrelor vs Clopidogrel | 2, 3, 7   |
| 7   | [26] | 2013 159 (62)           | ACS     | Ticagrelor vs Clopidogrel | 2       |
| 8   | [27] | 2007 984 (241)          | NSTE-ACS | Ticagrelor vs Clopidogrel | 1, 3, 4, 5, 6, 7 |
| 9   | [28] | 2009 18624 (4662)       | ACS     | Ticagrelor vs Clopidogrel | 1, 3, 4, 5, 6, 7 |
| 10  | [29] | 2014 160 (32)           | ACS     | Ticagrelor vs Clopidogrel | 1, 3, 4, 5, 6, 7 |
| 11  | [30] | 2014 63 (19)            | ACS     | Ticagrelor vs Clopidogrel | 3, 4       |
| 12  | [31] | 2015 114 (36)           | ACS     | Ticagrelor vs Prasugrel   | 3       |
| 13  | [32] | 2013 50 (9)             | STEMI   | Ticagrelor vs Prasugrel   | 2, 4, 5, 6, 7 |
| 14  | [33] | 2014 98 (31)            | Stable CAD | Ticagrelor vs Prasugrel   | 2       |
| 15  | [34] | 2015 55 (5)             | STEMI   | Ticagrelor vs Prasugrel   | 2, 3, 5   |
| 16  | [35] | 2009 101 (22)           | Stable CAD | Ticagrelor vs Clopidogrel | 2, 3, 7   |
| 17  | [36] | 2014 20 (6)             | ACS     | Ticagrelor vs Prasugrel   | 2       |
| 18  | [37] | 2012 44 (10)            | ACS & HTPR | T-P vs P-T       | 2, 3, 7   |
| 19  | [38] | 2015 40 (21)            | Stable CAD | T-C vs C-T       | 2, 7     |
| 20  | [39] | 2015 157 (157)          | STEMI with DM | Ticagrelor vs Clopidogrel | 3, 4, 5, 7 |
| 21  | [40] | 2015 120 (80)           | ACS     | Ticagrelor vs Clopidogrel | 7       |
| 22  | [41] | 2015 154 (154)          | STEMI with DM | Ticagrelor vs Clopidogrel | 3, 5, 7   |

Characteristics of included studies

a Outcomes: 1 incidence of composite endpoint; 2 platelet reactivity; 3 incidence of bleeding events; 4 incidence of myocardial infarction; 5 incidence of cardiovascular death; 6 incidence of stroke; 7 incidence of dyspnea

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random sequence generation, incomplete outcome data and selective reporting. Some studies did not mention allocation concealment, blinding of participants and personnel or random sequence generation. The other indexes of bias usually lacked specific description in the included clinical studies.

**Incidence of composite endpoint.** As far as general ACS patients are concerned, 5 studies, including a total of 33,258 patients, assessed the incidence of the composite endpoint. Low heterogeneity was shown among the studies \[P = 0.67, I^2 = 0\%\], and according to the fixed-effects model, the incidence of the composite endpoint in the ticagrelor group was significantly lower than the incidence in the clopidogrel group \[OR = 0.83, 95\%CI (0.77, 0.90), P < 0.00001\] (Fig 4). The funnel plot did not demonstrate publication bias \[P_{Pharbord} = 0.868\] (Fig 5A). A meta-regression analysis was conducted to evaluate the relationship between the DM patient proportion and the incidence of the composite endpoint. The result is shown in Fig 6A, which indicates that the incidence of the composite endpoint demonstrated no significant relationship with DM patient proportion \(P = 0.532\).

**Incidence of myocardial infarction.** 8 studies in general ACS patients comprising 33,282 patients were eligible for the final analysis. Low heterogeneity was shown among the studies \[P = 0.90, I^2 = 0\%\] and meta-analysis by fixed-effects model indicates that the incidence of myocardial infarction in the ticagrelor group is significantly lower than the incidence in the clopidogrel and prasugrel groups \[OR = 0.81, 95\%CI (0.74, 0.89), P < 0.0001\]. Subgroup analysis showed that the incidence of myocardial infarction in the ticagrelor group was significantly lower than the incidence in the clopidogrel group \[OR = 0.81, 95\%CI (0.74, 0.89), P = 0.0001\]. One study on prasugrel showed that the incidences of myocardial infarction were 0.0% and 3.9% in the ticagrelor and prasugrel groups, respectively (Fig 7A). The results showed signs of publication bias, as determined by the funnel plot in Fig 5B \(P_{Pharbord} = 0.005\). Meta-regression revealed that the results demonstrate no significant relationship between DM patient proportion and the occurrence of myocardial infarction \(P = 0.920\) (Fig 6B).

**Incidence of cardiovascular death.** Nine studies in general ACS patients comprising 33,369 patients were eligible for the final analysis. Heterogeneity was shown among the studies
| Study             | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|-----------|
| Alexopoulos 2012  | +                                           | +                                     | +                                                       | +                                             | +                                      | +                                   | Question |
| Alexopoulos 2012  | +                                           | ?                                     | +                                                       | +                                             | +                                      | ?                                   | Question |
| Alexopoulos 2014  | +                                           | +                                     | +                                                       | +                                             | ?                                      | ?                                   | +         |
| Angiolillo 2014   | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | Question |
| Cannon 2007       | +                                           | ?                                     | ?                                                       | ?                                             | ?                                      | +                                   | ?         |
| Cannon 2010       | +                                           | +                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Clavijo 2015      | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Gurbel 2009       | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Hansson 2014      | ?                                            | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Laine 2013        | +                                           | ?                                     | ?                                                       | +                                             | ?                                      | ?                                   | ?         |
| Laurent 2014      | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Li 2015           | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Liu 2014          | +                                           | ?                                     | ?                                                       | +                                             | ?                                      | ?                                   | ?         |
| Meng 2015         | ?                                            | ?                                     | ?                                                       | +                                             | ?                                      | ?                                   | ?         |
| Pan 2015          | ?                                            | ?                                     | ?                                                       | +                                             | ?                                      | ?                                   | ?         |
| Parodi 2013       | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Perl 2014         | ?                                            | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| T. Lhermusrer 2014| +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Waksman 2014      | +                                           | +                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Wallentin 2009    | +                                           | +                                     | +                                                       | ?                                             | ?                                      | ?                                   | Question |
| Yang 2013         | +                                           | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
| Zhang 2014        | ?                                            | ?                                     | +                                                       | +                                             | ?                                      | ?                                   | ?         |
[P = 0.06, I² = 46%], and the meta-analysis by random-effects model indicated that the incidence of cardiovascular death in the ticagrelor group was not significantly different from the incidence in the clopidogrel and prasugrel groups [OR = 0.93, 95%CI (0.73, 1.18), P = 0.55]. Subgroup analysis showed that the ticagrelor group had no significant difference form the clopidogrel [OR = 0.93, 95%CI (0.72, 1.20), P = 0.59] and prasugrel groups [OR = 0.70, 95%CI (0.11, 4.26), P = 0.70] (Fig 7B). The funnel plot in Fig 5C reveals that the results did not demonstrate publication bias (Pharbord = 0.282) and no significant relationship was found between DM patient proportion and the incidence of cardiovascular death by meta-regression (P = 0.446), as shown in Fig 6C.

**Incidence of stroke.** Four studies in general ACS patients comprising 32,853 patients were eligible for the final analysis. Low heterogeneity was shown among the studies [P = 0.95, I² = 0%] and meta-analysis by fixed-effects model indicates that the incidence of stroke in the ticagrelor group was not significantly different from the incidence in the clopidogrel group [OR = 1.14, 95%CI (0.93, 1.40), P = 0.20] (Fig 7C). The funnel plot in Fig 5D indicates no publication bias (Pharbord = 0.687) and no significant relationship was found between DM patient proportion and the occurrence of stroke by meta-regression (P = 0.716), as shown in Fig 6D.

**Platelet reactivity after 6 hours.** Five studies comprising 263 patients assessed platelet reactivity 6 hours after the administration of therapy in general ACS patients. High heterogeneity was shown among the studies [P < 0.00001, I² = 95%]. Thus, the random-effects model was used to evaluate the data, which showed that platelet reactivity 6 hours after the administration of therapy was not significantly different in the ticagrelor and control groups [MD = -45.45, 95%CI (-123.97, 33.07), P = 0.26] (Fig 8A). Further subgroup analysis showed no statistically significant difference between the ticagrelor group and the prasugrel group [MD = -3.65, 95%CI (-40.52, 33.22), P = 0.85]. One study on clopidogrel showed that both ticagrelor and clopidogrel inhibit platelet reactivity 6 hours after administration; the PRU values were 34.5 and 219.3, respectively (Fig 8A). No publication bias was observed, as determined by the funnel plot shown in Fig 5E (PeggE = 0.256). Further meta-regression analysis was conducted to evaluate the correlation between DM patient proportion and platelet reactivity 6 hours after administration of therapy. The results are shown in Fig 6E, which indicates that platelet reactivity 6 hours after administration demonstrates a significant relationship with DM patient proportion (P = 0.044).

| Study or Subgroup | Ticagrelor Events | Ticagrelor Total | Clopidogrel Events | Clopidogrel Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|-------------------|------------------|-----------------|-------------------|------------------|--------|-------------------------------|-------------------------------|
| Cannon 2007       | 19               | 334             | 17                | 327              | 1.0%   | 1.10 [0.56, 2.16]             |                               |
| Cannon 2010       | 569              | 6732            | 668               | 6676             | 39.2%  | 0.83 [0.74, 0.93]             |                               |
| Hansson 2014      | 7                | 173             | 8                 | 232              | 0.4%   | 1.18 [0.42, 3.32]             |                               |
| Liu 2014          | 4                | 80              | 9                 | 80               | 0.5%   | 0.42 [0.12, 1.41]             |                               |
| Wallentin 2009    | 864              | 9333            | 1014              | 9291             | 58.8%  | 0.83 [0.76, 0.92]             |                               |
| Total (95% CI)    | 16652            | 16606           | 100.0%            |                  |        | 0.83 [0.77, 0.90]             |                               |

Total events: 1463, 1716
Heterogeneity: Chi² = 2.34, df = 4 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.86 (P < 0.00001)

Fig 4. Forest plot of incidence of composite endpoint in ticagrelor and clopidogrel group.
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Platelet reactivity after 8 hours. Four studies comprising 327 patients assessed platelet reactivity 8 hours after the administration of therapy in general ACS patients. Heterogeneity was shown among the studies [P<0.00001, I2 = 90%] and the random-effects model indicated that platelet reactivity 8 hours after the administration of ticagrelor was significantly lower than clopidogrel and prasugrel [MD = -47.28, 95%CI (-81.14, -13.43), P = 0.006]. Subgroup analysis showed that there was no significant difference in the inhibition of platelet reactivity in the ticagrelor group 8 hours after administration compared to the prasugrel group [MD = -53.57, 95%CI (-117.59, 10.10), P = 0.10]. One study on clopidogrel showed that both ticagrelor and clopidogrel inhibited platelet reactivity 8 hours after administration; the PRU were 179.29 and 214.27, respectively (Fig 8B). The funnel plot in Fig 5F indicates no publication bias (Pegger = 0.679). Meta-regression analysis demonstrated that platelet reactivity 8 hours after the administration of therapy shows a significant relationship with DM patient proportion (P = 0.045) (Fig 6F).

Platelet reactivity at maintenance dose. Six studies comprising 440 patients assessed platelet reactivity at maintenance doses in general ACS patients. Heterogeneity was shown...
among the studies \(P = 0.0001, \text{I}^2 = 81\%\), and the random-effects model indicated that platelet reactivity in the ticagrelor group was significantly lower than platelet reactivity in the clopidogrel and prasugrel groups \(\text{MD} = -53.78, 95\%\text{CI} (-73.73, -33.82), \text{P} < 0.00001\). Subgroup analysis showed that the ticagrelor group demonstrated less platelet reactivity than the prasugrel group \(\text{MD} = -44.59, 95\%\text{CI} (-59.16, -30.02), \text{P} < 0.00001\). One study on clopidogrel showed that both ticagrelor and clopidogrel inhibit platelet reactivity at maintenance doses; the PRU were 34.7 and 154.7, respectively (Fig 8C). The funnel plot in Fig 5G indicates no publication bias \(\text{P} = 0.222\). Furthermore, meta-regression analysis shows no significant relationship between DM patient proportion and platelet reactivity at maintenance doses \(\text{P} = 0.965\) (Fig 6G).

**Incidence of bleeding events.** The data from 13 studies comprising 33,675 general ACS patients were eligible for incidence of bleeding events analysis and subgroup analysis. As shown in Fig 9A, low heterogeneity was shown among the studies \(P = 0.60, \text{I}^2 = 0\%\) and the pooled outcome of the fixed-effects model indicated that the incidence of bleeding events in the ticagrelor group was not significantly different from the incidence in the clopidogrel and
prasugrel groups [OR = 1.03, 95%CI (0.96, 1.11), P = 0.39]. Subgroup analysis showed that the ticagrelor group had no significant difference from the clopidogrel [OR = 1.03, 95%CI (0.96, 1.10), P = 0.46] and prasugrel groups [OR = 2.23, 95%CI (0.78, 6.32), P = 0.13]. Signs of publication bias were observed, as determined by the funnel plot shown in Fig 5H (Phar- bord = 0.003). Furthermore, no significant relationship was found between DM patient proportion and the incidence of bleeding by meta-regression (P = 0.744) (Fig 6H).

Incidence of dyspnea. Twelve studies comprising 20,072 general ACS patients were applicable for incidence of dyspnea analysis and subgroup analysis. As indicated in Fig 9B, low het- erogeneity was shown among the studies [P = 0.44, I² = 0%], and the meta-analysis by fixed-effects model indicated that the incidence of dyspnea in the ticagrelor group was significantly higher than the incidence in the clopidogrel and prasugrel groups [OR = 1.92, 95%CI (1.75, 2.11), P < 0.00001]. Subgroup analysis showed that the incidence of dyspnea in the ticagrelor

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Fig 7. Forest plots of MI, CVD and stroke. (A) Incidence of myocardial infarction; (B) Incidence of cardiovascular death; (C) Incidence of stroke.
group was significantly higher than the incidence in the clopidogrel [OR = 1.90, 95%CI (1.73, 2.08), P < 0.00001] and prasugrel groups [OR = 13.99, 95%CI (2.58, 75.92), P = 0.002]. The funnel plot in Fig 5I shows that the results demonstrated publication bias (Pharbord = 0.02); meta-regression revealed that the results did not demonstrate a significant relationship between DM patient proportion and the incidence of dyspnea (P = 0.160) (Fig 6I).

Discussion

Ticagrelor is a novel reversible platelet inhibitor that is notable for its superior clinical efficacy and safety [42]. The results of our preliminary research show that DM patients may represent a high-risk population for angiocardiopathy and the clinical efficacy of ticagrelor in this group differs from the overall cohort. Thus, it was important to evaluate the efficacy and safety of ticagrelor in DM patients. In this study, we conducted a systematic evaluation to assess the efficacy and safety of ticagrelor in general ACS patients and DM patients who were suffering from ACS. Although the 22 included RCTs comprise 35,004 participants, the various studies focused on different clinical indexes. Therefore, the primary endpoint was the incidence of the
composite endpoint (5 studies, 33,258 cases, containing the probability of any myocardial infarction, cardiovascular death or stroke). The secondary endpoints were the incidence of myocardial infarction (8 studies, 33,282 cases), the incidence of cardiovascular death (9 studies, 33,369 cases), the incidence of stroke (4 studies, 32,853 cases) and platelet reactivity (11 studies, 916 cases). The incidence of bleeding events (13 studies, 33,675 cases) and the incidence of dyspnea (12 studies, 20,072 cases) were used as safety endpoints.

Dosing is a crucial tissue in our research, and the conventional dosage of ticagrelor (90 mg bid) used in most of the clinical trials is based on the PLATO study (a phase III clinical study). Dosing in the PLATO study was based on the pharmacodynamics, efficacy and safety data demonstrated in the phase II study, these results indicated that a dose of 90 mg is well tolerated, acceptably safe and maximizes the inhibition of platelet aggregation [15]. Furthermore, higher doses of ticagrelor were not recommended, because the greatest suppression of platelet aggregation was seen at a dose of 90 mg. A lower dose of ticagrelor was not recommended because at lower doses the variability of platelet aggregation inhibition is more pronounced. In light of these two findings, we selected a dosage of 90 mg bid ticagrelor as an inclusion criterion for our study.

### Table 3.1: Ticagrelor vs Clopidogrel

| Study | Ticagrelor | Clopidogrel OR Prasugrel |
|-------|------------|--------------------------|
| Odds Ratio | Odds Ratio |
| Weight | Weight |
| 3.4.1 Ticagrelor vs Clopidogrel |
| Cannon 2007 | 34 | 334 | 257 | 1.89 (0.97, 3.69) |
| Cannon 2010 | 669 | 6995 | 6985 | 40.0% (0.29, 86.6) |
| Gurbel 2009 | 19 | 54 | 7 | 90.0% | 2.86 (0.87, 0.44) |
| Hansson 2014 | 166 | 173 | 213 | 232 | 0.5% | 2.10 (0.67, 7.15) |
| Li 2013 | 6 | 79 | 7 | 78 | 0.7% | 0.63 (0.27, 2.05) |
| Liu 2014 | 4 | 88 | 2 | 80 | 0.5% | 2.08 (0.37, 11.64) |
| Merg 2015 | 12 | 79 | 32 | 75 | 0.5% | 1.96 (0.47, 2.88) |
| Walker 2000 | 951 | 9239 | 9220 | 1.03 (0.54, 1.14) |
| Zhang 2014 | 5 | 81 | 3 | 32 | 0.5% | 1.50 (0.95, 2.35) |
| Subtotal (95% CI) | 1686 | 16864 | 95.7% | 1.03 (0.95, 1.11) |

Fig 9: Forest plots of safety endpoint. (A) Incidence of bleeding events; (B) Incidence of dyspnea.

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composite endpoint (5 studies, 33,258 cases, containing the probability of any myocardial infarction, cardiovascular death or stroke). The secondary endpoints were the incidence of myocardial infarction (8 studies, 33,282 cases), the incidence of cardiovascular death (9 studies, 33,369 cases), the incidence of stroke (4 studies, 32,853 cases) and platelet reactivity (11 studies, 916 cases). The incidence of bleeding events (13 studies, 33,675 cases) and the incidence of dyspnea (12 studies, 20,072 cases) were used as safety endpoints.

Dosing is a crucial tissue in our research, and the conventional dosage of ticagrelor (90 mg bid) used in most of the clinical trials is based on the PLATO study (a phase III clinical study). Dosing in the PLATO study was based on the pharmacodynamics, efficacy and safety data demonstrated in the phase II study, these results indicated that a dose of 90 mg is well tolerated, acceptably safe and maximizes the inhibition of platelet aggregation [15]. Furthermore, higher doses of ticagrelor were not recommended, because the greatest suppression of platelet aggregation was seen at a dose of 90 mg. A lower dose of ticagrelor was not recommended because at lower doses the variability of platelet aggregation inhibition is more pronounced. In light of these two findings, we selected a dosage of 90 mg bid ticagrelor as an inclusion criterion for our study.
The duration of dual antiplatelet therapy also has an impact on efficacy and safety. In our study, the duration of antiplatelet therapy in the included studies was less than 12 month. However, the research of Fabrizio D’Ascenzo [43] noted that long-term usage (12 months or more) of dual antiplatelet therapy may increase the risk of bleeding events. Therefore, in this meta-analysis, the incidence of bleeding events was considered an important endpoint for the safety investigation of ticagrelor in general ACS and DM patients.

In this research, ticagrelor reduced the incidence of the composite endpoint in general ACS patients compared to clopidogrel, and these results were in accordance with the conclusions drawn in both the PLATO study [21] [9.0% vs 10.7%, 95%CI (0.75, 0.94), P = 0.0025] and in Wallentin’s research [28] [9.8% vs 11.7%, 95%CI (0.77, 0.92), P<0.001]. Both demonstrated that ticagrelor may significantly reduce the rate of myocardial infarction, death from vascular causes and the incidence of stroke.

As for secondary endpoints, ticagrelor may reduce the incidence of myocardial infarction compared to clopidogrel and prasugrel [OR = 0.81, 95%CI (0.74, 0.89), P<0.0001]. Ticagrelor did not statistically reduce the incidence of cardiovascular death compared to either clopidogrel or prasugrel [OR = 0.93, 95%CI (0.73, 1.18), P = 0.55]. Furthermore, ticagrelor did not significantly reduce the incidence of stroke compared to clopidogrel [OR = 1.14, 95%CI (0.93, 1.40), P = 0.20]. According to the research of Thibault Lhermusier, ticagrelor showed stronger inhibition of platelet reactivity in ACS patients compared to prasugrel [MD: -42.5, 95% CI: -62.9, -21.9] and was more effective than regular doses [MD: -139.7, 95% CI: -182.6, -136.6] or high doses [MD: -125.5, 95% CI: -154.9, -96.4] of clopidogrel [12]. The results of this study further supported the evidence presented above. Compared with clopidogrel and prasugrel, ticagrelor did not significantly reduce platelet reactivity after 6 hours [MD = -45.45, 95%CI (-123.97, 33.07), P = 0.26], but a significant reduction of platelet reactivity was found in the ticagrelor group after 8 hours [MD = -47.28, 95%CI (-81.14, -13.43), P = 0.006] and during the period of maintenance dosing [MD = -53.78, 95%CI (-73.73, -33.82), P<0.00001]. The results above demonstrate that the efficacy of ticagrelor is superior to the efficacy of clopidogrel or prasugrel in long-term treatment.

Ticagrelor did not statistically reduce the incidence of bleeding events compared with clopidogrel and prasugrel [OR = 1.03, 95%CI (0.96, 1.11), P = 0.39]. These results were also supported by the PRAGUE-18 Study (Zuzana Motovska, 2016) [44], which noted the head-to-head comparison of prasugrel and ticagrelor failed to show that one was more effective than the other in preventing bleeding events, including TIMI and BARC bleeding events. Furthermore, in Chirag’s research [45], ticagrelor showed a non-significant increase in TIMI major bleeding [OR = 1.14, 95%CI (0.74, 1.75), P = 0.10] and TIMI major/minor bleeding [OR = 1.07, 95%CI (0.97, 1.18), P = 0.89] compared with clopidogrel. These results were in accordance with our research.

Moreover, it is also worth noting that ticagrelor can significantly increase the incidence of dyspnea compared with clopidogrel and prasugrel. It may be that ticagrelor causes an increase in the endogenous adenosine concentration [46, 47] and the inhibition of P2Y_{12} on sensory neurons [48].

Based on the above results, meta-regression analysis was used to describe the difference in efficacy and safety of ticagrelor between diabetes mellitus patients and general ACS patients. There was no difference between general ACS patients and DM patients in reducing the incidence of the composite endpoint in the ticagrelor group. Meanwhile, the incidences of myocardial infarction, cardiovascular death and stroke showed no significant differences between general ACS patients and DM patients. However, the period of platelet reactivity recovery in DM patients was shorter than that of general ACS patients, which probably contributed to the higher platelet reactivity of DM patients with ACS. Nevertheless, in long-term usage, a non-significant difference in platelet reactivity was found between DM patients and general ACS patients.
patients. Furthermore, a non-significant difference was found between DM patients and general ACS patients in the incidence of bleeding events and dyspnea.

Our meta-regression analysis was also supported by the subgroup analysis of the PLATO study (4,662 patients with pre-existing DM and 13,951 patients without DM), which showed that the benefits and risks of ticagrelor in DM patients coincided with the outcomes of the cohort. Moreover, ticagrelor reduced the composite endpoints of cardiovascular death, myocardial infarction or stroke, and all-cause death in DM patients, without increasing the risk of bleeding. Low heterogeneity was present in general ACS and DM patients [2].

Nevertheless, it was noted that potential publication bias might exist in our study because it was a literature-based analysis, and a large proportion of the included publications showed positive results.

In conclusion, according to the existing research, ticagrelor exhibits superior clinical efficacy and safety than either clopidogrel or prasugrel in treating ACS. In the subgroup of DM patients, the clinical efficacy and safety of ticagrelor showed no obvious difference. However, the platelet reactivity of DM patients should be monitored in the treatment of ACS. Furthermore, more multi-center RCTs are required to ensure the reliability of these data and guide clinical practice.

Supporting information
S1 File. PRISMA 2009 checklist.
(PDF)
S1 Fig. Search strategy of this study.
(TIF)

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References
1. Alexopoulos D, Xanthopoulou I, Mavronasiou E, Stavrou K, Siapika A, Tsoni E, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with diabetes. Diabetes care.
2. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontry F, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATElet inhibition and patient Outcomes (PLATO) trial. European heart journal. 2010; 31(24):3006–16. Epub 2010/08/31. PubMed Central PMCID: PMCPMC3001588. https://doi.org/10.1093/eurheartj/ehq325 PMID: 20802246

3. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. American heart journal. 2009; 157(4):599–605. https://doi.org/10.1016/j.ahj.2009.01.003 PMID: 19332184

4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. The New England journal of medicine. 2001; 345(7):494–502. Epub 2001/08/25. https://doi.org/10.1056/NEJMoa010746 PMID: 11519503

5. Kassimis G, Davlouros P, Xanthopoulou I, Stavrou EF, Athanassiadou A, Alexopoulos D. CYP2C19 and other genetic variants affecting platelet response to clopidogrel in patients undergoing percutaneous coronary intervention. Thrombosis research. 2012; 129(4):441–6. Epub 2011/08/13. https://doi.org/10.1016/j.thromres.2011.07.022 PMID: 21831410

6. Brandt JT, Close SL, Iturria SJ, Payne CD, Farid NA, Ernest CS 2nd, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. Journal of thrombosis and haemostasis: JTH. 2007; 5(12):2429–36. Epub 2007/09/29. https://doi.org/10.1111/j.1538-7836.2007.02775.x PMID: 17900275

7. Kazui M, Nishiya Y, Ishizuka T, Hagi kara K, Farid NA, Okazaki O, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. Drug metabolism and disposition: the biological fate of chemicals. 2010; 38(9):92–9.

8. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. The New England journal of medicine. 2007; 357(20):2001–15. Epub 2007/11/06. https://doi.org/10.1056/NEJMoa0706482 PMID: 17982182

9. Springthorpe B, Bailey A, Barton P, Birkinshaw TN, Brown RC, et al. From ATP to AZD6140: the discovery of an orally active reversible P2Y12 receptor antagonist for the prevention of thrombosis. Bioorganic & medicinal chemistry letters. 2007; 17(21):6013–8.

10. Husted S, van Giezen JJ. Ticagrelor: the first reversibly binding oral P2Y12 receptor antagonist. Expert opinion on pharmacotherapy. 2013; 14(2):237–45. Epub 2012/12/28. https://doi.org/10.1517/14656566.2013.757303 PMID: 23268703

11. Htun WW, Steinshlub SR. Ticagrelor: the first novel reversible P2Y(12) inhibitor. Expert opinion on pharmacotherapy. 2013; 14(2):237–45. Epub 2012/12/28. https://doi.org/10.1517/14656566.2013.757303 PMID: 23268703

12. Lhermusier T, Lipinski MJ, Tantry US, Escarcega RO, Baker N, Bilen KP, et al. Meta-analysis of direct and indirect comparison of ticagrelor and prasugrel effects on platelet reactivity. The American journal of cardiology. 2015; 115(6):716–23. https://doi.org/10.1016/j.amjcard.2014.12.029 PMID: 25728845

13. Biondi-Zoccai G, Lotrionte M, Agostoni P, Abbate A, Romagnoli E, Sangiorgi G, et al. Adjusted indirect comparison meta-analysis of prasugrel versus ticagrelor for patients with acute coronary syndromes. International journal of cardiology. 2011; 150(3):325–31. https://doi.org/10.1016/j.ijcard.2010.08.035 PMID: 20828843

14. Chatterjee S, Ghose A, Sharma A, Guha G, Mukherjee D, Frankel R. Comparing newer oral anti-platelets prasugrel and ticagrelor in reduction of ischemic events-evidence from a network meta-analysis. Journal of thrombosis and thrombolysis. 2013; 36(3):223–32. https://doi.org/10.1007/s11239-012-0838-z PMID: 23212803

15. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of Platelet Aggregation by AZD6140, A Reversible Oral P2Y12 Receptor Antagonist, Compared With Clopidogrel in Patients With Acute Coronary Syndromes. Journal of the American College of Cardiology. 2007; 50(19):1852–6. https://doi.org/10.1016/j.jacc.2007.07.058 PMID: 17980251

16. Vazzana N, Ranalli P, Cuccurullo C, Davi G. Diabetes mellitus and thrombosis. Thrombosis research. 2012; 129(3):371–7. https://doi.org/10.1016/j.thromres.2011.11.052 PMID: 22197180

17. Preis SR, Hwang SJ, Coady S, Pencina MJ, D’Agostino RB Sr., Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the United States. JAMA. 2013; 36(8):2211–6. PubMed Central PMCID: PMC3714492. https://doi.org/10.1023/d012-2510 PMID: 23491524
De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009; 339:b4531. PubMed Central PMCID: PMC2774388. https://doi.org/10.1136/bmj.b4531

18. Bhatt DL, Eagle KA, Ohman EM, Hirsh AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA. 2010; 304(12):1350–7. Epub 2010/09/02. https://doi.org/10.1001/jama.2010.1322 PMID: 20805624

19. De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009; 339:b4531. PubMed Central PMCID: PMC2774388. https://doi.org/10.1136/bmj.b4531 PMID: 19897665

20. Gu H, Wang Y, Li W. The application of cochrane risk of bias tools in meta-analysis of RCT. Chinese Circulation Journal. 2014; 29(02):147–8.

21. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuels H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet (London, England). 2010; 375(9711):283–93. Epub 2010/01/19.

22. Laine M, Frere C, Toesca R, Berbis J, Barnay P, Pansieri M, et al. Ticagrelor versus prasugrel in diabetic patients with an acute coronary syndrome. A pharmacodynamic randomised study. Thrombosis and haemostasis. 2014; 111(2):273–8. https://doi.org/10.1160/TH13-05-0384 PMID: 24154787

23. Hansson EC, Rexius H, Dellborg M, Albertsson P, Jeppsson A. Coronary artery bypass grafting-related bleeding complications in real-life acute coronary syndrome patients treated with clopidogrel or ticagrelor. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery. 2014; 46(4):699–705; discussion

24. Waksman R, Maya J, Angiolillo D, Carlsson G, Teng R, Caplan R, et al. Ticagrelor Versus Clopidogrel in African American Patients with Coronary Artery Disease and Diabetes Mellitus. Journal of the American College of Cardiology. 2014; 63(12):A211.

25. Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome. Journal of the American College of Cardiology. 2014; 63(9):872–7. https://doi.org/10.1016/j.jacc.2013.09.067 PMID: 24291273

26. Yang X, Zhang J, Yi F, Liu H, Wang H, Li C. Effect of ticagrelor on patients undergoing percutaneous coronary intervention with acute coronary syndrome. Chin J Clinicians(Electronic Edition). 2013; 7(19):8696–700.

27. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. Journal of the American College of Cardiology. 2007; 50(19):1844–51. https://doi.org/10.1016/j.jacc.2007.07.053 PMID: 17980250

28. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine. 2009; 361(11):1045–57. https://doi.org/10.1056/NEJMoa0904327 PMID: 19717846

29. Liu D, Wang Z. The application of ticagrelor for elderly patients with percutaneous coronary intervention in ST-segment elevation myocardial infarction. Chinese Journal of Gerontology. 2014; (10):2638–41.

30. Zhang Y, Zhang H, Zhao Y, Pang M, Wu Y, Zhao C, et al. The application of ticagrelor on the elderly patients with acute coronary syndrome. Chinese Journal of Gerontology. 2014; 34(06):1450–2.

31. Peri L, Zemer-Wassercug N, Rechavia E, Vaduganathan M, Orvin K, Weissler-Snr A, et al. Comparison of platelet inhibition by prasugrel versus ticagrelor over time in patients with acute myocardial infarction. Journal of thrombosis and thrombolysis. 2015; 39(1):1–7. https://doi.org/10.1007/s11239-014-1119-9 PMID: 25085573

32. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. Journal of the American College of Cardiology. 2013; 61(15):1601–6. https://doi.org/10.1016/j.jacc.2013.01.024 PMID: 23500251

33. Angiolillo DJ, Curzen N, Gurbel P, Vaitkus P, Lipkin F, Li W, et al. Pharmacodynamic evaluation of switching from ticagrelor to prasugrel in patients with stable coronary artery disease: Results of the SWAP-2 Study (Switching Anti Platelet-2). Journal of the American College of Cardiology. 2014; 63(15):1500–9. https://doi.org/10.1016/j.jacc.2013.11.032 PMID: 24333493

34. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circulation Cardiovascular interventions. 2012; 5(6):797–804. https://doi.org/10.1161/CIRCINTERVENTIONS.112.972323 PMID: 23169985
35. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. 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. https://doi.org/10.1161/CIRCULATIONAHA.109.912550 PMID: 19923168

36. Lhermusier T, Voisin S, Murat G, Mejean S, Garcia C, Bataille V, et al. Switching patients from clopidogrel to novel P2Y12 receptor inhibitors in acute coronary syndrome: comparative effects of prasugrel and ticagrelor on platelet reactivity. International journal of cardiology. 2014; 174(3):874–6. https://doi.org/10.1016/j.ijcard.2014.04.208 PMID: 24820749

37. Alexopoulos D, Galati A, Xanthopoulou I, Mavronasiou E, Kassimis G, Theodoropoulos KC, et al. Ticagrelor versus prasugrel in high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. Journal of the American College of Cardiology. 2012; 60(3):193–9. https://doi.org/10.1016/j.jacc.2012.03.060 PMID: 22789884

38. Clavijo LC, Maya J, Carlson G, Angiolillo DJ, Teng R, Caplan R, et al. Platelet inhibition with ticagrelor versus clopidogrel in Hispanic patients with stable coronary artery disease with or without diabetes mellitus. Cardiovascular revascularization medicine: including molecular interventions. 2015; 16(8):450–4.

39. Li X, Dong G, Chen M. The cardioprotective effect of ticagrelor for patients with ST-segment elevation acute coronary syndrome and diabetes. Guangdong Medical Journal. 2015; 36(08):1257–60.

40. Pan C, Hu Z, Wang B. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and diabetes mellitus. Acta Universitatis Medicinalis Anhui. 2015;(09):1351–3.

41. Meng X, Meng H, Liu H, Chen Y. Effects of ticagrelor on patients with ST-segment elevation myocardial infarction and diabetes undergoing percutaneous coronary intervention. Chin Hosp Pharm J. 2015; 35(15):1406–9.

42. Zhang X, Ke Y. Clinical research of new type P2Y12 receptor inhibitor ticagrelor. Chin J Clin Pharmacol Ther. 2014;(04):459–64.

43. D’Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, et al. Meta-Analysis of the Duration of Dual Antiplatelet Therapy in Patients Treated With Second-Generation Drug-Eluting Stents. The American journal of cardiology. 2016; 117(11):1714–23. https://doi.org/10.1016/j.amjcard.2016.03.005 PMID: 27134057

44. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, et al. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation. 2016; 134(21):1603–12. https://doi.org/10.1161/CIRCULATIONAHA.116.024823 PMID: 27576777

45. Bavishi C, Panwar S, Messerli FH, Bangalore S. Meta-Analysis of Comparison of the Newer Oral P2Y12 Inhibitors (Prasugrel or Ticagrelor) to Clopidogrel in Patients With Non-ST-Elevation Acute Coronary Syndrome. The American journal of cardiology. 2015; 116(5):809–17. https://doi.org/10.1016/j.amjcard.2015.05.088 PMID: 26119655

46. Belchikov YG, Koenig SJ, Dipasquale EM. Potential role of endogenous adenosine in ticagrelor-induced dyspnea. Pharmacotherapy. 2013; 33(8):882–7. https://doi.org/10.1002/phar.1293 PMID: 23712633

47. Cattaneo M, Schulz R, Nylander S. Adenosine-mediated effects of ticagrelor: evidence and potential clinical relevance. Journal of the American College of Cardiology. 2014; 63(23):2503–9. https://doi.org/10.1016/j.jacc.2014.03.031 PMID: 24788973

48. Cattaneo M, Faioni EM. Why does ticagrelor induce dyspnea? Thrombosis and haemostasis. 2012; 108(6):1031–6. https://doi.org/10.1160/TH12-08-0547 PMID: 23070079