Platelet inhibition and clinical outcomes of low dose ticagrelor in patients with coronary artery disease: a meta-analysis of randomized controlled trials

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Research Article

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Abstract

Background

Although current guidelines recommend ticagrelor 90 mg twice daily in ACS patients for 12 months and 60 mg twice daily in stable patients 1 to 3 years after MI with additional high-risk features, the bleeding complication was actually higher than clopidogrel. This meta-analysis was performed to assess the platelet inhibition and clinical outcomes of low dose ticagrelor in patients with CAD.

Methods

Medline, EMBASE and Cochrane Databases were systematically searched from inception to March, 2021 for randomized controlled trials (RCTs) comparing low dose ticagrelor with standard dose clopidogrel or standard dose ticagrelor in patients with CAD. Pooled estimates were calculated using fixed-effects or random-effects model as appropriate.

Results

15 RCTs that included 15357 patients were identified. Low dose ticagrelor had no statistical differences of the risks of MACE and major bleeding compared with standard dose ticagrelor and standard dose clopidogrel (RR 0.98, 95%CI 0.87 − 1.11, P = 0.80; RR 1.35, 95%CI 0.46 − 4.00, P = 0.59; RR 0.86, 95%CI 0.68 − 1.10, P = 0.23; RR 1.46, 95%CI 0.45 − 4.76, P = 0.53, respectively). Compared with standard dose clopidogrel, low dose ticagrelor showed significantly lower platelet reaction units (PRU) (MD -118.48, 95%CI -144.33−-92.63, P < 0.00001), rates of high on-treatment platelet reactivity (HTPR) (RR 0.10, 95%CI 0.04 − 0.21, P < 0.00001) and minor or minimal bleeding (RR 0.73, 95%CI 0.55 − 0.96, P = 0.03), but increased the incidence of dyspnea (RR 6.48, 95%CI 1.78 − 23.54, P = 0.005). Compared with standard dose ticagrelor, low dose ticagrelor showed significantly higher PRU (MD 15.45, 95%CI 5.45 − 25.44, P = 0.002) and risk of dyspnea (RR 0.81, 95%CI 0.75 − 0.88, P < 0.00001), but similar rates of HTPR (RR 1.63, 95%CI 0.40 − 6.70, P = 0.50) and minor or minimal bleeding (RR 1.36, 95%CI 0.78 − 2.38, P = 0.28).

Conclusion

Low dose ticagrelor may provide an additional choice for secondary prevention in CAD patients. However, the specific dose of ticagrelor should be selected according to the patients' clinical characteristics.

Introduction

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS) [1].

Ticagrelor is a reversible non-thienopyridine oral $P2Y_{12}$ inhibitor that provides faster, more potent and consistent platelet inhibition than clopidogrel [2]. The PLATO trial demonstrated in patients who have an ACS, treatment with ticagrelor 90 mg twice daily as compared with clopidogrel 75 mg once daily significantly reduced the rate of ischemic complications without an increase in the rate of overall major bleeding [3]. In the PEGASUS-TIMI 54 study of post-MI patients with additional high-risk features and low bleeding risks, the benefit-to-risk profile appears to be numerically more favorable for ticagrelor 60 mg twice daily [4]. In this, the current guidelines recommend ticagrelor 90 mg twice daily in ACS patients for 12 months and 60 mg twice daily in MI patients with high ischaemic-risk who have tolerated dual antiplatelet therapy (DAPT) without a bleeding complication for longer than 12 months [5–7].

However, antithrombotic therapy for patients with CAD is a long-term management. The optimal antiplatelet therapy aims to prevent thrombosis while avoiding hemorrhage. To account for this, different strategies have been proposed, such as de-escalation strategy [8] and platelet function [9] or genotype-guided strategy [10]. Recently, several studies have displayed low dose ticagrelor could provide better safety and tolerability than standard usage of ticagrelor while achieving greater and more consistent platelet inhibition than standard usage of clopidogrel [11–13]. Therefore, we conducted a meta-analysis to assess the platelet inhibition and clinical outcomes of low dose ticagrelor in patients with CAD.

Methods

Literature Search

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We systematically searched Medline, EMBASE and Cochrane Databases for all relevant articles comparing low dose ticagrelor with standard dose clopidogrel or standard dose ticagrelor in patients with CAD through March, 2021. Literature was searched with the following keywords: ticagrelor, AZD6140, AZD 6140, AZD-6140, 30, 45, 60, quarter, half, low, reduced, once, coronary disease, coronary artery disease, coronary heart disease, acute coronary syndrome, myocardial infarction, unstable angina, chronic coronary syndromes and random*. A comprehensive search of reference lists of all review articles and original studies retrieved by this method was performed to identify additional studies.

Selection criteria

The inclusion criteria were the following: (1) trials designed as RCT; (2) trials based on patients with CAD; (3) trials compared low dose ticagrelor with standard dose clopidogrel or standard dose ticagrelor; (4) trials reported outcomes included platelet inhibition, ischemic events or bleeding events.

Data Abstraction

Two investigators (Cheng Xie and Xiaoliang Ding) independently assessed studies for possible inclusion by reading titles and/or abstracts, then viewed the full-texts of the remaining publications to pick up the ultimately available studies. Data extraction was done by one reviewer (Cheng Xie), and subsequently cross-checked by the other reviewer (Xiaoliang Ding). Any divergences were discussed or determined by a third investigator (Qiong Qin). Following information was abstracted: the first author and publication year, country, sample size, baseline features of patients, intervention features, follow-up time, platelet inhibition and clinical outcomes and their definitions.

Bias Risk and Study Quality Assessment

The methodological quality of eligible studies was assessed by the Cochrane collaboration's tool for assessing risk of bias including the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. The bias risk of each study was scored as low, unclear, or high in each section.

Statistical Analysis

Dichotomous data were expressed risk ratio (RR) with 95% confidence interval (CI). Continuous data were expressed as mean difference (MD). Heterogeneity of effect size across the studies was tested using Q statistics at the $P < 0.10$ level of significance. We also calculated the I^2 statistic with a quantitative measure of inconsistency across the studies. The data were pooled by random-effects model in case significant heterogeneity (Cochran test with $P < 0.10$ or $I^2 > 50\%$) was found. Otherwise, the fixed-effects model was used. Sensitivity analyses with fixed-effect models were performed to assess consistency among effect estimates that were obtained with random- and fixed-effects models. Meta-analysis was performed with the software of Cochrane Review Manager 5.1.2 (Cochrane Library Software, Oxford, UK).

Results

Study selection and study characteristics

Fig. 1 shows a flow diagram for the selection process. A total of 15 RCTs [4, 11-24] that included 15357 patients (low dose ticagrelor = 7582, standard dose ticagrelor = 416, standard dose clopidogrel = 7445) were finally identified. Table 1 summarizes the characteristics of the selected studies. Among the 15 RCTs, ten studies were based on patients from East Asia [11, 15-18, 21, 22-24] and the others were from Poland [13], Greece [20], United Kingdom and United States [4, 12, 19]. The low doses of ticagrelor investigated in these studies were different, six studies used 60 mg twice daily [4, 11, 12, 13, 19, 20, 22], five studies used 45 mg twice daily [14, 15, 17, 23, 24], the other four studies used 22.5 mg twice daily [16], 60 mg once daily [22], 45 mg twice daily and 60 mg twice daily [18], and 45 mg twice daily and 90 mg once daily [21], respectively. The characteristics of the included studies were shown in Tab. 1. Quality assessments for studies are reported in Supplemental Fig. S1 and S2.

Platelet inhibition

13 studies reported platelet inhibition [11-22, 24] and VerifyNow P2Y12 assay was the most widely reported method [11, 12, 16, 17, 19-22]. Pooled analysis indicated that compared with standard dose ticagrelor, low dose ticagrelor showed significantly higher platelet reaction units (PRU) (MD 15.45, 95%CI 5.45–25.44, P = 0.002). Even so, the PRU of low dose ticagrelor was significantly lower than standard dose clopidogrel (MD -118.48, 95%CI -144.33–-92.63, P 0.00001) (Fig. 2).

9 studies reported the rates of high on-treatment platelet reactivity (HTPR) [11-13, 16, 17, 19-22]. Pooled analysis indicated that low dose ticagrelor had similar rate of HTPR compared with standard dose ticagrelor (RR 1.63, 95%CI 0.40–6.70, P = 0.50), but significantly lower than standard dose clopidogrel (RR 0.10, 95%CI 0.04–0.21, P 0.00001) (Fig. 3).

Clinical efficacy

6 studies [4, 12, 13, 20, 23, 24] reported major adverse cardiovascular events (MACE). Pooled analysis indicated that compared with standard dose ticagrelor and standard dose clopidogrel, low dose ticagrelor had similar risk of MACE (RR 0.98, 95%CI 0.87–1.11, P = 0.80 and RR 1.35, 95%CI 0.46–4.00, P = 0.59, respectively) (Fig. 4).

Clinical safety

13 studies [4, 12-18, 20-24] reported bleeding events. Pooled analysis indicated that compared with standard dose ticagrelor and standard dose clopidogrel, low dose ticagrelor had similar risk of major bleeding (RR 0.86, 95%CI 0.68–1.10, P = 0.23 and RR 1.46, 95%CI 0.45–4.76, P = 0.53, respectively) (Fig. 5). In terms of minor or minimal bleeding, low dose ticagrelor significantly reduced the incidence compared with standard dose ticagrelor (RR 0.73, 95%CI 0.55–0.96, P = 0.03). Meanwhile, it did not significantly increase the incidence compared with standard dose clopidogrel (RR 1.36, 95%CI 0.78–2.38, P = 0.28) (Fig. 6).

12 studies [4, 12-18, 20-22, 24] reported the adverse drug reaction of dyspnea. Pooled analysis indicated that compared with standard dose ticagrelor, low dose ticagrelor significantly reduced the incidence of dyspnea (RR 0.81, 95%CI 0.75–0.88, P 0.00001), but compared with standard dose clopidogrel it significantly increased the incidence (RR 6.48, 95%CI 1.78–23.54, P = 0.005) (Fig. 7).

Sensitivity analyses

There was no difference in the results between the fixed-effect model and the random-effect model for the platelet inhibition and clinical outcomes.

Discussion

Antiplatelet agents are the cornerstone of secondary prevention in patients with CAD. Ticagrelor has the most predictable and consistently high level of P2Y12 inhibition during maintenance therapy, and also has more rapid onset, as well as more rapid and predictable offset of action compared with clopidogrel [25, 26]. How to reduce thrombotic complications while minimizing the occurrence of bleeding and other adverse events is the hotspot of current antiplatelet therapy. In this meta-analysis, we assessed the platelet inhibition and clinical outcomes of low dose ticagrelor in patients with CAD. The main findings of this meta-analysis were as follows: (1) Although the PRU of low dose ticagrelor was significantly higher than standard dose ticagrelor, the rate of HTPR was similar, and both of them were significantly lower than standard dose clopidogrel. (2) Compared with standard dose ticagrelor and standard dose clopidogrel, low dose ticagrelor had similar risks of MACE and major bleeding, but the incidence of minor or minimal bleeding was significantly lower than standard dose ticagrelor. (3) The rate of dyspnea of low dose ticagrelor was significantly lower than standard dose ticagrelor, but significantly higher than standard dose clopidogrel.

Plaque rupture and thrombosis are the major concerns in patients with CAD, and excessive platelet activation and aggregation are central to the pathogenesis of CAD. Although correlations between various platelet function assays were not robust, the most widely used assays such as VerifyNow P2Y12 assay have overcome many of the technical and methodological limitations of previous assays [27, 28]. In the past decades, compelling evidence from numerous observational studies has emerged demonstrating a strong association between HTPR and ischemic events [29, 30].

Bleeding, as the most common side effects of ticagrelor, has been well evaluated in previous studies. Although both the PLATO trial [3] and PEGASUS-TIMI 54 trial [4] demonstrated ticagrelor achieved greater reduction of MACE, at the expense of more non-fatal bleeding and dyspnoea. The recent completion of RCTs comparing ticagrelor with clopidogrel, specifically dedicated to the evaluation of those

particular patient populations, such as elderly [31] or Asian patients [32], found clopidogrel is a favourable alternative to ticagrelor, because it leads to fewer bleeding events without an increase in the combined endpoint of MACE. Combined with the results of our meta-analysis, low dose ticagrelor may provide an additional antiplatelet strategy to balance the risk of ischemia and bleeding.

Dyspnea was another important side effect of ticagrelor. The PLATO trial showed that dyspnea was more common in the ticagrelor group than in the clopidogrel group (13.8% vs. 7.8%, P < 0.001) and more patients discontinued treatment (0.9% vs. 0.1%, P < 0.001). Zhang et al. did a meta-analysis including 21 RCTs showed ticagrelor was associated with an increased risk of dyspnea compared with clopidogrel (RR 2.15, 95%CI 1.59–2.92, P < 0.01) and was consistent in subgroups with different follow-up durations [33]. On the other hand, the DISPERSE [34] and DISPERSE-2 [35] trial reported that the increased rate of dyspnea was dose-dependent. These results were consistent with our meta-analysis.

We acknowledge our meta-analysis had several limitations. First, various low doses of ticagrelor were included. Second, because of limited data, patients with ACS and CCS were pooled together. Third, given the limited number of studies included in the analysis, our findings should be confirmed with future research.

Conclusions

Low dose ticagrelor may provide an additional choice for secondary prevention in CAD patients. However, the specific dose of ticagrelor should be selected according to the patients' clinical characteristics.

Declarations

Authors contribution

CX and YZ contributed to the conception or design of the work. CX, XD and QQ contributed to the acquisition, analysis, or interpretation of data for the work. CX and XD drafted the manuscript. JL and YZ critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interests regarding the publication of this manuscript.

Ethical

Approval Not required.

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Table

Tab. 1 Characteristics of the included studies

Authors	Publication year	Country	Sample size (I/C)	Patients	Follow up	Age (I/C, years)	Male (I/C, %)	Smoking (I/C, %)	Hypertension (I/C, %)	Dyslipidemia (I/C, %)	Diabetes (I/C, %)	Intervention	HTPR criteria	Bleeding criteria
Hiasa Y, et al [14]	2014	Japan/ Philippines	139	3 months post PCI or ACS	28d	63±11/64±10	92/83	NA	58/65	52/50	16/26	45mg BID	—	PLATO
Bonaca MP, et al [4]	2015	United Kingdom/ United States	14095	1 to 3 years post MI	33m	65.2±8.4/65.4±8.4	76.4/76.1	17.1/16.8	77.5/77.5	76.4/76.7	32.8/31.8	60mg BID	—	TIMI
LI K, et al [15]	2015	China	351	UA	12m	62.1±6.9/62.4±5.8	72.2/72.1	43.6/46.0	53.8/52.3	36.1/37.8	39.8/42.3	45mg BID	—	PLATO
He M, et al [16]	2016	China	30	SCAD	7d	64.60±5.45	63.33	3.33	90	13.33	NA	22.5mg BID	PRU > 208	NA
Xue HJ, et al [17]	2016	China	61	NSTE-ACS	5d	60.35±8.59/59.95 ±9.87	60/70	25/50	35/60	50/30	NA	45mg BID	PRU > 208	PLATO
Li H, et al [18]	2016	China	36	SCAD	7d	59.3±9.8/57.9±12.6	NA	NA	NA	NA	NA	45mg BID	—	NA
						61.3±7.0/57.9±12.6	NA	NA	NA	NA	NA	60mg BID	—	NA
Storey RF, et al [19]	2016	United Kingdom/ United States	116	1 to 3 years post MI	28d	63.3±6.6/64.2±6.9	91/83	16/19	45/52	NA	35/11	60mg BID	PRU > 208	—
Alexopoulos D, et al [20]	2017	Greece	20	1 to 3 years post MI	14d	58.5±10.2	100	35	NA	NA	70	60mg BID	PRU > 208	BARC
Choi KN, et al [21]	2017	Korean	62	12 months post PCI	28d	63±12/65±7	70/68	30/23	60/41	5/18	25/18	45mg BID	PRU > 208	TIMI
						59±10/65±7	95/68	55/23	55/41	10/18	20/18	90mg QD	PRU > 208	TIMI
Park DW, et al [11]	2018	Korea	60	ACS	30d	NA	NA	NA	NA	NA	NA	60mg BID	PRU > 208	—
Orme RC, et al [12]	2018	United Kingdom	162	SCAD received PCI	30d	66.9±8.6/64.6±8.5	85/77	11/12	69/68	87/90	20/21	60mg BID	PRU > 208	PLATO
Kubica J, et al [13]	2019	Poland	52	30 days post AMI	14d	55.0±9.0/57.8±8.9	35/31	65/65	65/69	92/92	19/15	60mg BID	PRI > 50%	TIMI
He M, et al [22]	2020	China	36	CCS	7d	NA	NA	NA	NA	NA	NA	60mg QD	PRU > 235	NA
Xue J, et al [23]	2020	China	74	ACS	3m	NA	55/50	70/15	25/74	35/17	85/19	45mg BID	—	NA
Wang Y, et al [24]	2021	China	63	STEMI	6m	55.65±15.19/55.44±11.0	83.9/84.4	NA	61.3/56.3	NA	25.8/28.1	45mg BID	—	PLATO

Abbreviations: I: intervention group; C: control group; SCAD: stable coronary artery disease; NSTE-ACS: non-ST segment elevated acute coronary syndrome; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; CCS: chronic coronary syndrome; MI: myocardial infarction; UA: unstable angina; BID: bis in die; QD: quaque die; HTPR: high on-treatment platelet reactivity; PRU: platelet reaction units; PLATO: platelet inhibition and patient outcomes trial; TIMI: thrombolysis in myocardial infarction; BARC: bleeding academic research consortium; NA: not available; —: no data

Figures

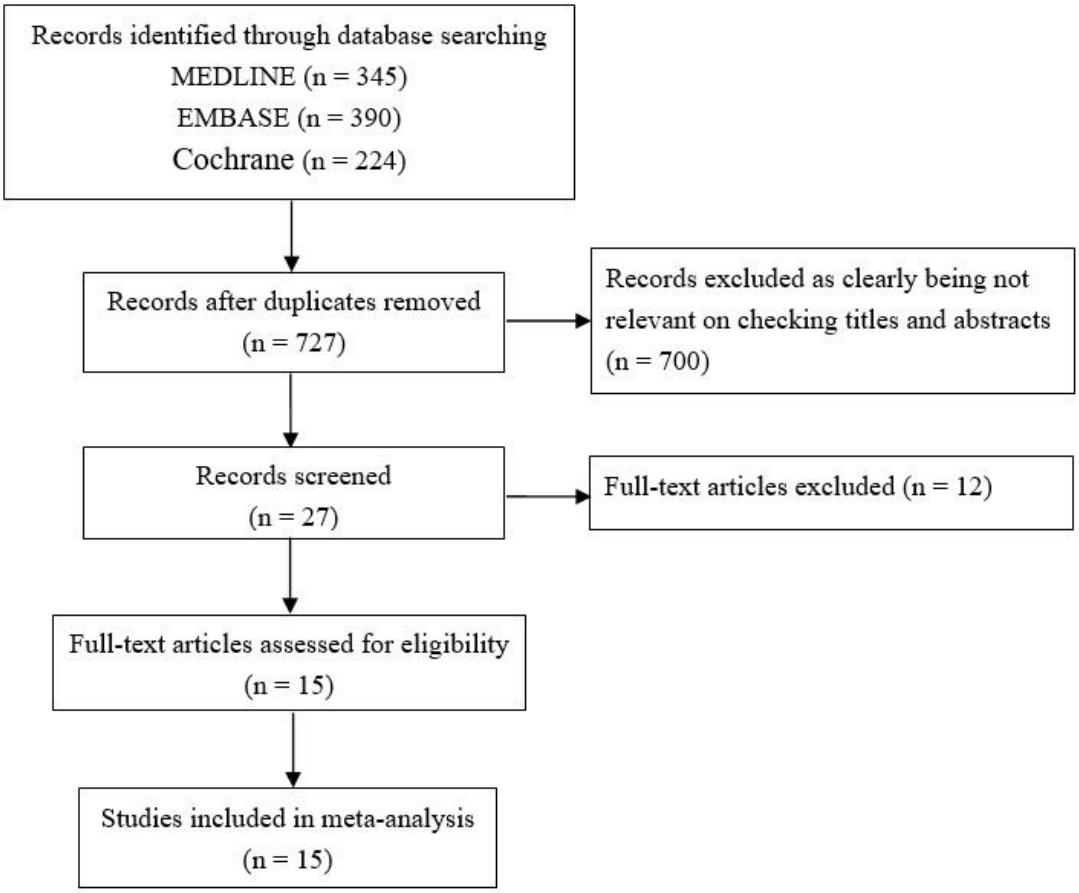

Figure 1

Study selection according to the PRISMA model

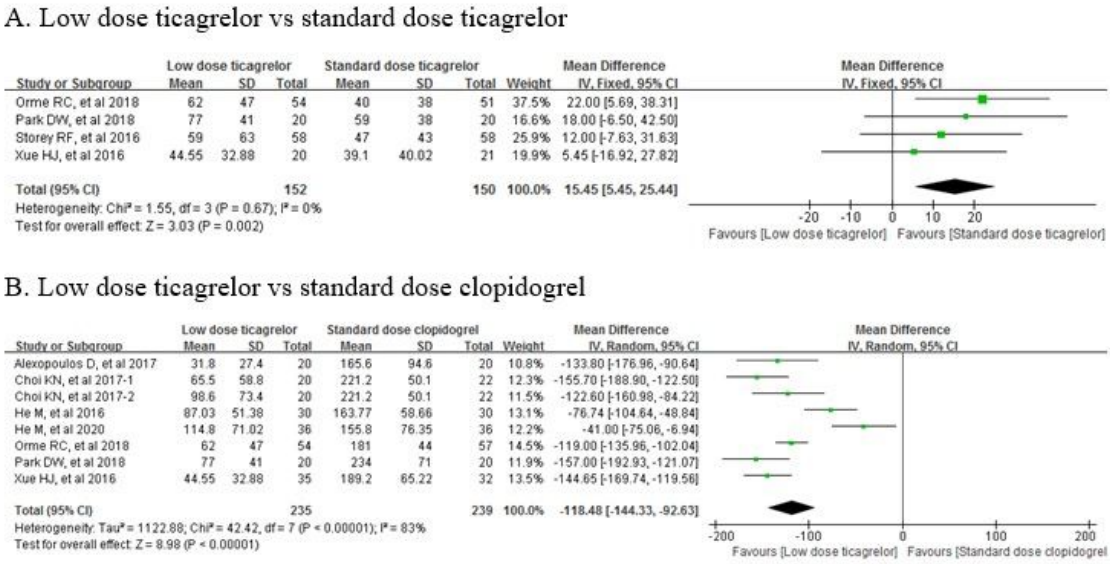

Figure 2

Forest plot of PRU

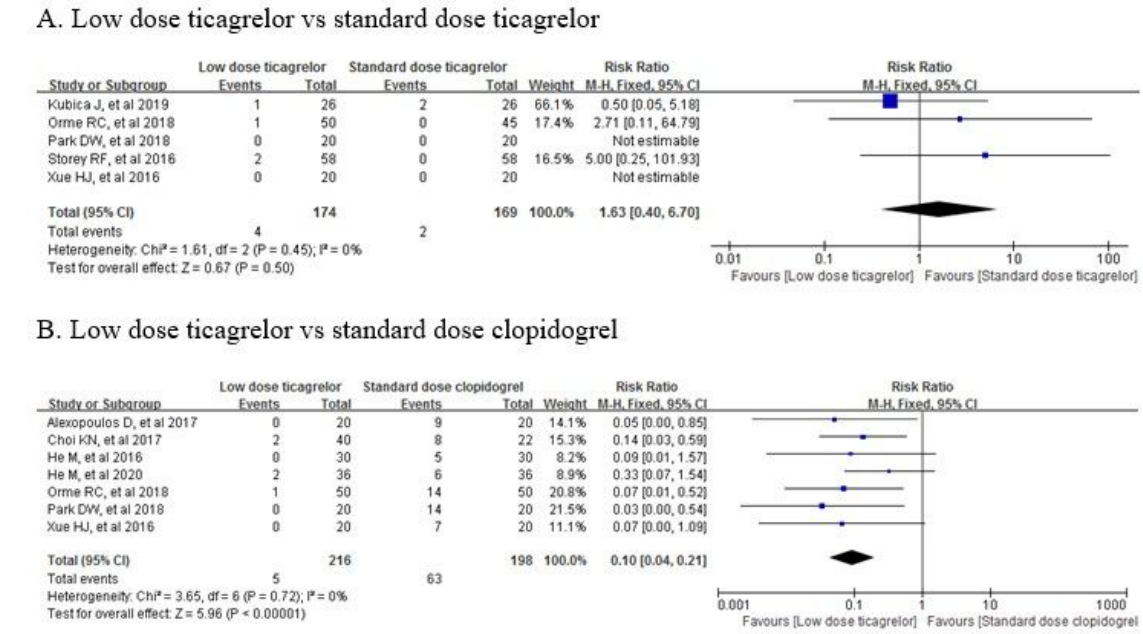

Figure 3

Forest plot of HTPR

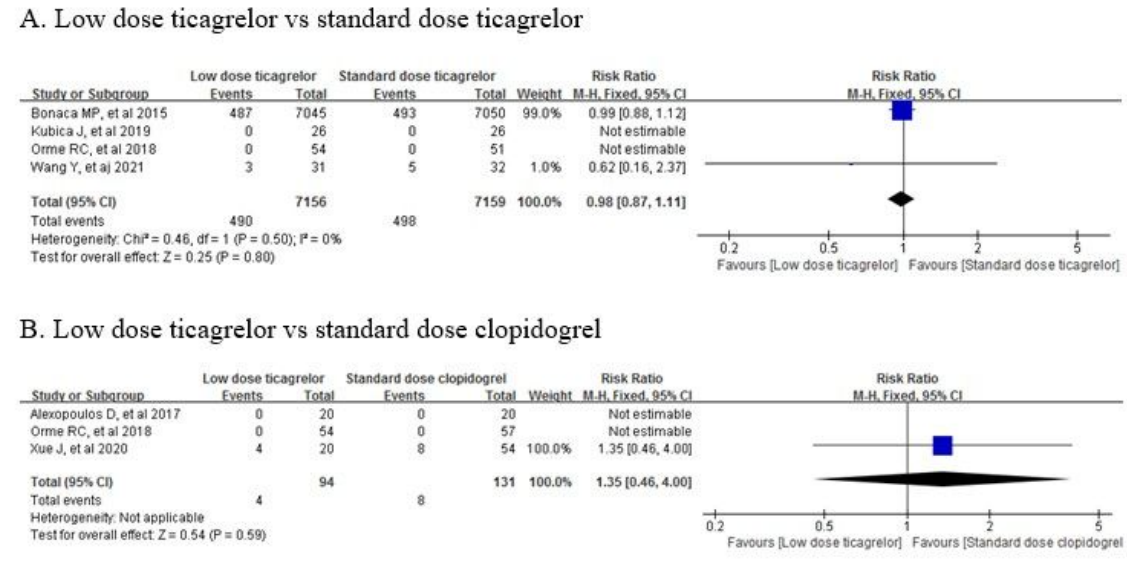

Figure 4

Forest plot of MACE

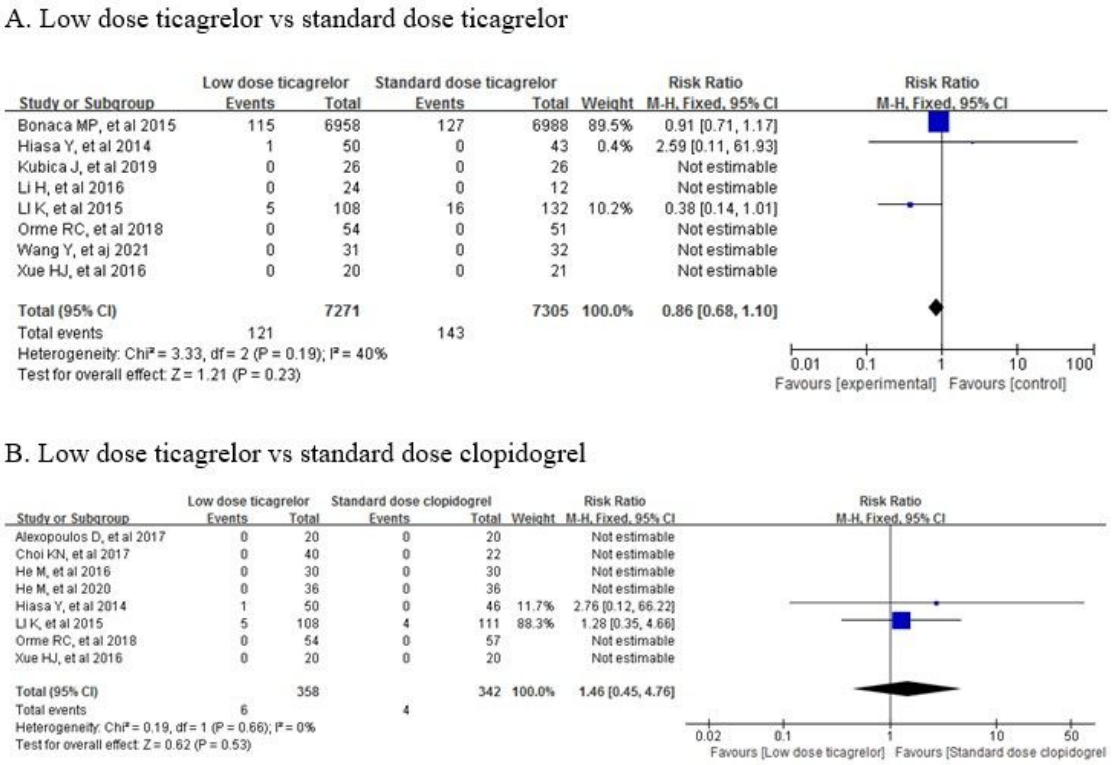

Figure 5

Forest plot of major bleeding

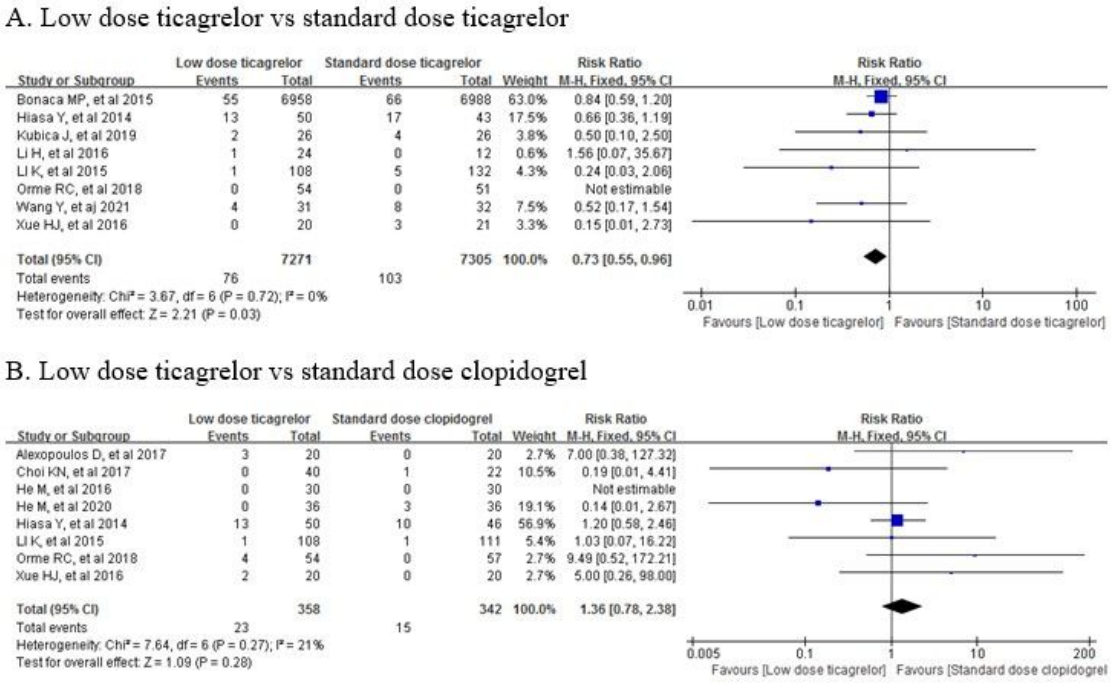

Figure 6

Forest plot of minor or minimal bleeding

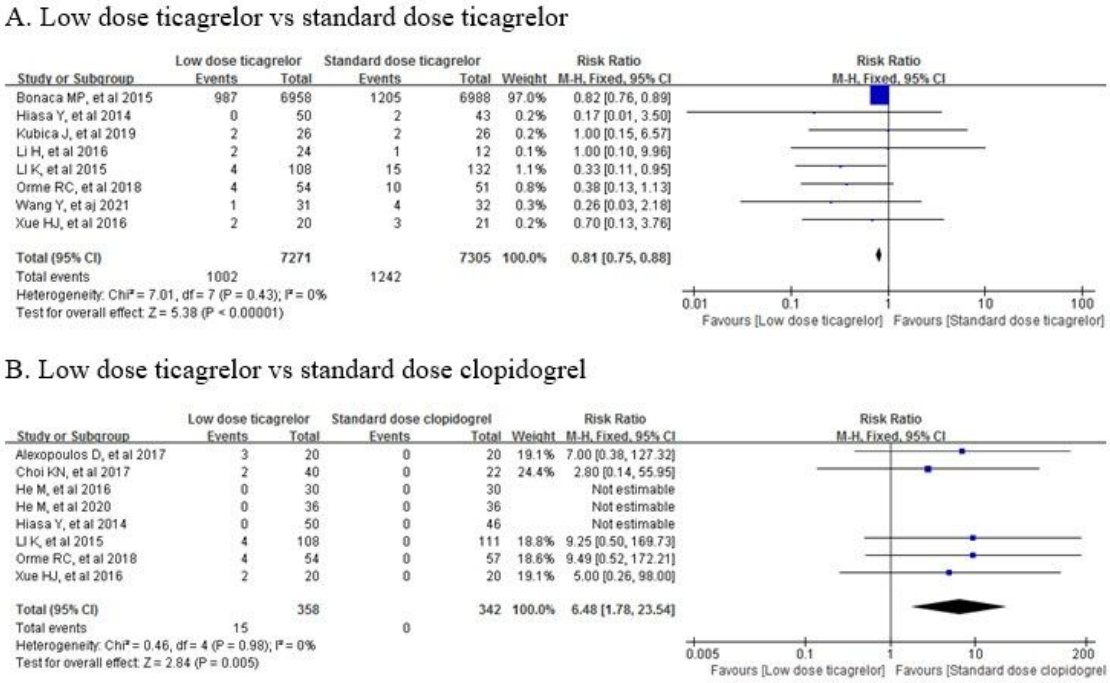

Figure 7

Forest plot of dyspnea

Supplementary Files

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- Supplemental.docx