ORIGINAL ARTICLE

TICAGRELOR VERSUS CLOPIDOGREL, DRUG OF CHOICE FOR THE PREVENTION OF STENT THROMBOSIS AFTER PERCUTANEOUS CORONARY INTERVENTION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Objectives: The objective of this meta-analysis of randomized controlled trials was to compare the efficacy of ticagrelor versus Clopidogrel for preventing stent thrombosis (ST) following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

Methodology: A comprehensive literature search was conducted using MEDLINE/PubMed, EMBASE, Web of Science, and the Cochrane Library. The inclusion criteria involved selecting randomized controlled trials that included patients with ACS undergoing PCI, comparing the use of ticagrelor and Clopidogrel, having a follow-up period of at least 30 days, and reporting data on ST. The meta-analysis was performed using the R statistical software version 4.1.1, and the "meta" package was utilized. The Mantel-Haenszel method was employed to calculate the relative risk (RR) and corresponding 95% confidence interval (CI) for comparing the risk of ST between the two treatment groups.

Results: A total of seven randomized controlled trials were included in the analysis, comprising a population of 28,609 patients with ACS who were randomized to receive either ticagrelor or Clopidogrel in a ratio of 12,116:16,493. The cumulative rate of ST was found to be 2.2% (185/8,423) in the ticagrelor group and 2.7% (347/12,851) in the clopidogrel group. The meta-analysis revealed a significant decrease in the rate of ST with ticagrelor compared to Clopidogrel, demonstrating a relative risk of 0.71 (95% CI: 0.59 to 0.85). No heterogeneity was detected among the included studies, as indicated by an I2 value of 0% and a p-value of 0.463.

Conclusion: In conclusion, the findings of this meta-analysis suggest that ticagrelor is a significantly more effective P2Y12 inhibitor than Clopidogrel for preventing ST following PCI in patients with ACS. These results support using ticagrelor as the preferred antiplatelet therapy in this patient population.

Keywords: meta-analysis, Ticagrelor, Clopidogrel, stent thrombosis, percutaneous coronary intervention, acute coronary syndrome

Citation: Ishaq M, Ashraf N, Chand G, Khatti S, Mueed A, Raheem A. Ticagrelor versus Clopidogrel, Drug of Choice for the Prevention of Stent Thrombosis after Percutaneous Coronary Intervention: A Meta-Analysis of Randomized Controlled Trials. Pak Heart J. 2023;56(02):140-145. DOI: https://doi.org/10.47144/phj.v56i2.2520

INTRODUCTION

Despite significant advancements in the rapid diagnosis and management of cardiovascular diseases (CVD), acute myocardial infarction (AMI) remains the most common clinical presentation of CVD, posing a high risk of premature mortality.[1] The current clinical practice guidelines from major societies recommend emergent/urgent percutaneous coronary intervention (PCI) using intracoronary stents as the first-line treatment for mechanical revascularization, particularly for patients with ST-segment elevation myocardial infarction (STEMI).[2,3] While stent technology has revolutionized interventional cardiology, the initial bare-metal stents (BMS) were associated with several complications.[4] Over time, the first-generation drug-eluting stents (G1-DES) reduced the risk of target lesion revascularization and in-stent restenosis compared to BMS. Still, concerns regarding late thrombotic events persisted until the development of second-generation drug-eluting stents (G2-DES).[5] G2-DES represents an improvement over G1-DES, with a reduced risk of late thrombotic events while maintaining similar anti-restenotic efficacy.[6]

Despite the advancements in stent technology, stent thrombosis remains a rare but life-threatening complication following stent deployment. It can occur

within the first 24 hours (acute), up to 30 days (sub-acute), or beyond 30 days (late) after stent placement.[7] Stent thrombosis involves a complex interplay of procedure-, lesion-, patient-, and post-procedure-related factors. While procedure and technique-related factors are more significant in early stent thrombosis, platelet activation plays a crucial role in its pathophysiology, making inhibition of platelet function a potential avenue for prevention.[8,9] Dual antiplatelet therapy (DAPT), which combines a P2Y12 inhibitor with aspirin, is recommended to prevent stent thrombosis.[10] Popular choices for P2Y12 inhibitors include Clopidogrel, Prasugrel, and Ticagrelor. However, clinicians must carefully balance the prevention of stent thrombosis with the risk of bleeding associated with these antiplatelet agents.[11] Discontinuation of DAPT during the early phases of stent deployment can have catastrophic consequences and is a common factor that can trigger early stent thrombosis.[7]

While Clopidogrel is commonly used as a P2Y12 inhibitor, Ticagrelor offers a new alternative with stronger and faster inhibitory effects on platelets. It has been reported to be safe and effective in preventing major adverse cardiovascular events (MACE) in patients with acute coronary syndrome.[12,13] However, it is crucial to re-evaluate the two agents to prevent stent thrombosis, particularly in the context of primary PCI. Therefore, this meta-analysis of randomized controlled trials aims to compare the efficacy of Ticagrelor versus Clopidogrel in preventing stent thrombosis after PCI in patients with acute coronary syndrome (ACS).

METHODOLOGY

The following methodology was employed to conduct the meta-analysis in accordance with the PRISMA ("Preferred Reporting Items for Systematic Reviews and Meta-Analyses") guidelines.[14]

Literature Search Strategy:

Two independent investigators conducted a comprehensive search for relevant publications using four electronic databases: MEDLINE/PubMed, EMBASE, Web of Science, and the Cochrane Library. A uniform search string was used across all platforms, including terms such as "acute coronary syndrome," "ACS," "acute myocardial infarction," "AMI," "percutaneous coronary intervention," "PCI," "dual antiplatelet therapy," "DAPT," "Clopidogrel," "Ticagrelor," and "stent thrombosis." Additionally, the official websites of prominent cardiology-related journals were searched to identify potentially relevant literature.

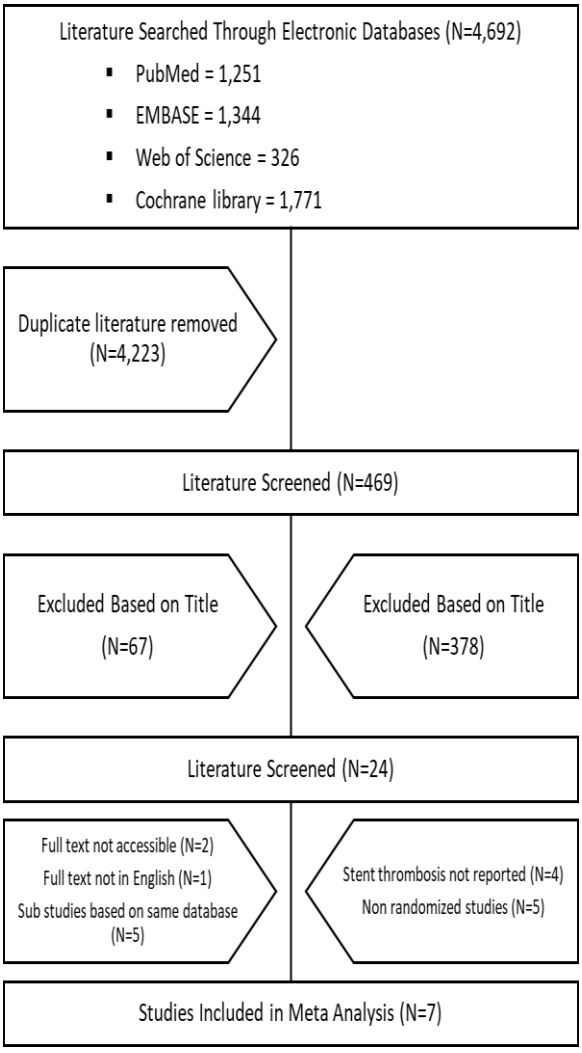

Figure 1: Study Selection Flow Chart:
A flowchart was created to illustrate the study selection process, including the number of records identified, records screened, full-text articles assessed for eligibility, and final studies included in the analysis.

Literature Selection Criteria:

The inclusion criteria for the meta-analysis were as follows: randomized controlled trials that enrolled patients with acute coronary syndrome undergoing PCI, a comparison of Ticagrelor and Clopidogrel as first-line DAPT, a minimum follow-up period of 30 days, and reporting of stent thrombosis (acute, sub-acute, or late) as a clinical endpoint. Studies such as meta-analyses, observational studies, case series, and those needing a head-to-head comparison between Ticagrelor and Clopidogrel, as well as studies not reporting stent thrombosis as an outcome of interest, manuscripts in languages other than English, Furthermore, sub-group analyses of previously

reported trials were excluded to avoid duplication of patient data.

Assessment of Study Quality:

The methodological quality of the included studies was evaluated using the Jadad scoring system, which assesses randomization, blinding, and withdrawals/dropouts.[15] The Jadad score ranges from 0 to 5, with a score of 3 or higher indicating good quality. Two independent investigators assessed the quality of each included trial, and any disagreements were resolved through discussion or consultation with a third investigator.

Outcome of Interest:

The primary outcome of interest was stent thrombosis (ST), categorized as acute, sub-acute, or late, based on the criteria defined by the Academic Research Consortium.

Statistical Analysis:

The meta-analysis was conducted using the open-source software R version 4.1.1, with the "meta" package utilized for the analysis. The Mantel-Haenszel method was employed to calculate the relative risk (RR) and the corresponding 95% confidence interval (CI) for comparing the risk of stent thrombosis between Ticagrelor and Clopidogrel. Heterogeneity among the included studies was assessed using Higgins' and Thompson's I2 and Cochran's Q statistics. In the absence of significant heterogeneity, a fixed-effect model was employed to estimate the pooled effect size.

RESULTS

A comprehensive search using the predefined search string yielded a total of 4,692 articles, which were subsequently screened for eligibility. After removing duplicates and applying inclusion criteria, 91 articles underwent abstract review, resulting in the exclusion of 67 articles. Finally, 24 articles were selected for full-text review. However, full-text access was unavailable for two articles, and one was written in Chinese, resulting in their exclusion. Among the remaining articles, five were excluded due to reporting sub-group analyses, not reporting stent thrombosis as an outcome, or being non-randomized studies. Ultimately, seven randomized controlled trials were included in the analysis, comprising a total of 21,274 patients with acute coronary syndrome (ACS), with a ratio of 8,423 patients receiving Ticagrelor and 12,851 patients receiving Clopidogrel. The follow-up duration varied from 30 days to 12 months (Table 1).

Table 1: Study characteristics of the included randomized controlled trials

Serial	Trial	Population	Quality	Participants		Follow-up
				Ticagrelor	Clopidogrel	
1	PLATO 2009[16]	ACS	5	5,640	5,649	12 months
2	Tang et al. 2016[17]	STEMI	3	200	200	6 months
3	Zhang et al. 2016[18]	ACS	4	91	90	6 months
4	Chen et al. 2017[19]	ACS/Stable CAD	3	57	46	5.5 months
5	Liu et al. 2017[20]	Diabetic STEMI	4	86	85	30 days
6	Li et al. 2018[21]	STEMI	4	161	281	12 months
7	Welsh et al. 2019[22]	STEMI	5	2188	6500	1 year

The mean age of patients ranged from 59 to 69 years in the Ticagrelor group and from 59 to 72 years in the Clopidogrel group. Table 2 provides the distribution of patients' medical history and clinical characteristics in the included trials for both Ticagrelor and Clopidogrel groups.The cumulative rate of stent thrombosis was found to be 2.2% (185/8,423) in the Ticagrelor group and 2.7% (347/12,851) in the Clopidogrel group. A significant decrease in the rate of stent thrombosis was observed with Ticagrelor compared to Clopidogrel, with a relative risk of 0.71 [95% CI: 0.59 to 0.85], as depicted in Figure 2. No heterogeneity was detected among the included studies, with an I2 value of 0% and $p = 0.463$.

Table 2: Distribution of patients' medical history and clinical characteristics among included trial

Trial	Age (years)		Female		Hypertension		Diabetes mellitus		Smoker		ST-elevation MI	
	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel	Ticagrelor	Clopidogrel
PLATO 2009[16]	62	62	2655	2633	6139	6044	2326	2336	3360	3318	3496	3530
Tang et al. 2016[17]	64	64	58	54	122	116	58	42	116	124	200	200
Zhang et al. 2016[18]	69	72	49	41	35	37	34	31	13	13	26	23
Chen et al. 2017[19]	61	60	23	17	32	25	18	11	20	15	-	-
Liu et al. 2017[20]	59	59	23	28	44	47	86	85	37	42	86	85
Li et al. 2018[21]	60	63	25	71	78	162	45	67	101	165	161	281
Welsh et al. 2019[22]	-	-	484	1560	962	3443	332	1224	945	3001	2188	6500

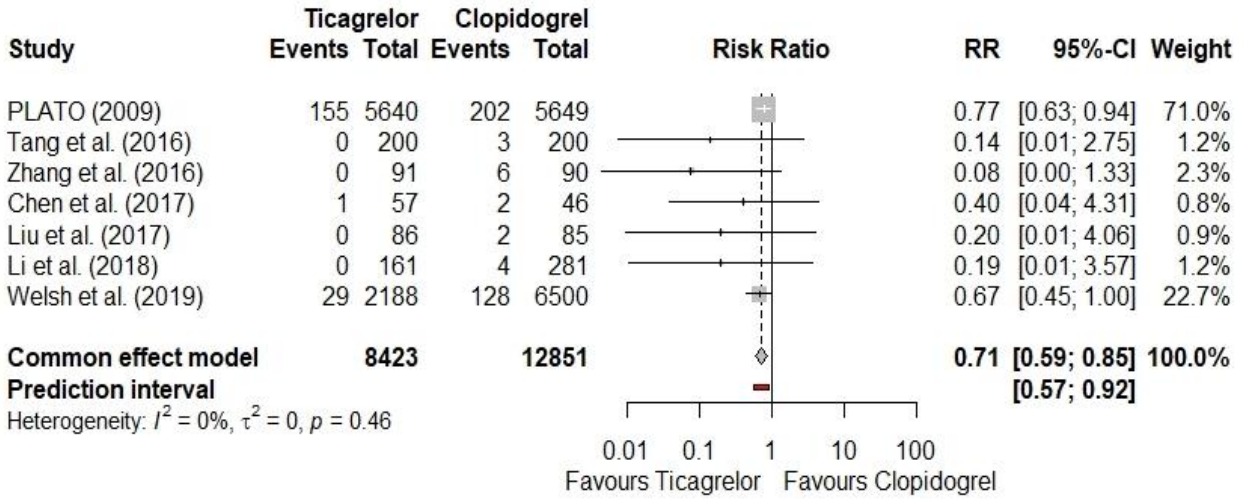

Figure 2: Forest plot comparing the efficacy of ticagrelor and Clopidogrel for the prevention of stent thrombosis after PCI in patients with ACS

DISCUSSION

Dual antiplatelet therapy (DAPT) is recommended for preventing stent thrombosis after stent placement. Clopidogrel, a commonly used P2Y12 inhibitor, has been compared to ticagrelor in multiple randomized controlled trials (RCTs), consistently demonstrating ticagrelor's superior efficacy.[16-22] In this meta-analysis, we aimed to assess the effectiveness of ticagrelor compared to Clopidogrel in preventing stent thrombosis after percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS).

Our findings support previous meta-analyses that have reported better efficacy of ticagrelor in preventing stent thrombosis after PCI. For instance, Fan ZG et al.[13] conducted a comprehensive meta-analysis comparing the risk of stent thrombosis as a secondary outcome. Their analysis, including 2 RCTs and three non-randomized studies, reported a relative risk of 0.74 [95% CI: 0.59-0.93] in favor of ticagrelor compared to Clopidogrel. Yoon HY et al.[23] also observed a significant decline in stent thrombosis with ticagrelor compared to Clopidogrel, with a relative risk of 0.55 [95% CI: 0.41-0.74] in their sub-analysis of 8 randomized and non-randomized studies. Chen W et al.[24] conducted a network meta-analysis of 14 studies, reporting similar efficacy between prasugrel and ticagrelor, but both were more effective than Clopidogrel in preventing stent thrombosis. However, Guan W et al.[12] reported no significant difference between ticagrelor and Clopidogrel in their meta-analysis of multiple randomized and non-randomized studies, with a relative risk of 0.70 [95% CI: 0.47-1.05].

In our meta-analysis, the PLATO trial[16] carried the highest weight, accounting for 71.0% due to its large sample size. Consistent with other trials, PLATO reported a significantly lower rate of stent thrombosis with ticagrelor than Clopidogrel, with rates of 1.3% and 1.9%, respectively (p=0.01). The trial by Welsh et al.[22] had the second largest weight, accounting for 22.7%, and showed rates of stent thrombosis at 2.0% for ticagrelor and 1.4% for Clopidogrel.

However, it is worth noting that recent real-world observational and registry-based studies have reported conflicting results, suggesting the non-superiority of ticagrelor over Clopidogrel in preventing stent thrombosis.[25-27] These studies often highlight lower compliance with ticagrelor outside the controlled setting of RCTs, primarily due to financial concerns, the need for twice-daily dosing, and increased risk of complications. These factors may have influenced the observed efficacy of ticagrelor in real-world practice.[24]

Several limitations should be acknowledged in our meta-analysis. Firstly, the included trials had varying study populations, potentially introducing heterogeneity in patient characteristics and baseline risk factors for stent thrombosis. Furthermore, the lack of uniformity in the definition and categorization criteria for stent thrombosis among the trials might have affected the consistency of the reported outcomes. The type of stent used in each trial is also an important confounding factor, as different stent types carry varying risks of stent thrombosis. Moreover, the variable lengths of follow-up among the included trials may have impacted the detection and reporting of stent thrombosis rates. Finally, the primary outcome of interest was not stent thrombosis for most of the included trials. This might have resulted in underpowered analyses to detect differences in stent thrombosis rates between the study groups.

CONCLUSION

In conclusion, this meta-analysis demonstrates that Ticagrelor is significantly more effective than Clopidogrel in preventing stent thrombosis after PCI in patients with ACS. The findings contribute to the existing body of evidence supporting the superiority of Ticagrelor as a first-line DAPT agent in this clinical setting. However, it is essential to consider the limitations of this analysis, including the heterogeneity among the included trials, potential variations in stent types, and inconsistent definitions of stent thrombosis. Future studies addressing these limitations could further strengthen the evidence base for optimizing antiplatelet therapy in patients undergoing PCI for ACS.

AUTHORS' CONTRIBUTION

MI and NA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. GC, SK, AM, and AR: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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