

Effect of Pre-Hospital Ticagrelor in Primary Percutaneous Coronary Intervention on Patients with ST-Segment Elevation Myocardial Infarction: A systematic review and meta-analysis

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Abstract

Objective: To determine the therapeutic effects of pre-admission ticagrelor in acute ST elevation myocardial infarction after primary percutaneous coronary intervention.

Methods: The meta analysis was conducted at the period from the establishment of the database to the February 2018 period, and comprised earlier studies that were selected after comprehensive search of PubMed, Medline, Excerpta Medica dataBASE and Cochrane databases. The studies compared the pre-treatment group (pre-hospital ticagrelor) with the control group (in-hospital ticagrelor) and found differences in primary percutaneous coronary intervention outcomes for sick individuals suffering from acute ST elevation myocardial infarction.

Results: The two studies selected together had 1915 subjects. The rate of stent thrombosis in the control group was higher than in the pre-treatment group ($p < 0.01$), but there were no significant differences in all-cause mortality ($p = 0.88$), myocardial infarction ($p = 0.17$) and stroke ($p = 0.49$).

Conclusions: Pre-hospital ticagrelor decreased the incidence of stent thrombosis in patients with acute ST elevation myocardial infarction who underwent primary percutaneous coronary intervention.

Keywords: Pre-hospital, Ticagrelor, Percutaneous coronary intervention, PCI, Myocardial infarction, MI, Stent thrombosis, Meta. (JPMA 69: 1343; 2019)

Introduction

The advantages of ticagrelor treatment before being admitted to a hospital in primary percutaneous coronary intervention (PPCI) individuals suffering from ST-segment elevation myocardial infarction (STEMI) are unclear and controversial. The usual view is that the early anti-thrombotic therapy can increase the coronary re-canalisation rate and reduce coronary thrombus burden, thereby reducing all-cause mortality.¹⁻⁴ In sick individuals suffering from acute myocardial infarction (AMI), the benefits of anti-coagulant and thrombolytic therapy are clear.⁵ However, in PPCI-sick individuals suffering from STEMI, per-admission ticagrelor-inhibiting platelet aggregation seems to be of little benefit, and some of the results are harmful.⁶ Pre-hospital ticagrelor not only reduces stent thrombosis after PPCI, but also does not increase all-cause mortality or the rate of new MIs.⁷ In this way, pre-hospital ticagrelor for PPCI-patients suffering from STEMI is considerably beneficial. The

current meta analysis was planned to determine the effect of ticagrelor before being admitted to the hospital in PPCI patients suffering from STEMI.

Materials and Methods

The meta analysis was conducted at the period from the establishment of the database to the February 2018 period, and comprised earlier studies that were selected after comprehensive search of PubMed, Medline, Excerpta Medica dataBASE (EMBASE) and Cochrane databases. The search was not limited by language. Medical Subject Heading (MeSH) terms and key words were employed to identify literature covering PPCI, Primary percutaneous coronary intervention and Ticagrelor. The study was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.⁸

The search comprised randomised controlled trials (RCTs) and prospective cohort studies performed on PPCI patients suffering from STEMI.⁹ Inclusion criteria for study selection comprised acute STEMI diagnosis, first loading dose of ticagrelor >30 min before undergoing PPCI, and

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maintenance dose of 90mg ticagrelor two times a day. Studies involving patients presenting more than 12h after the onset of symptoms, patients treated with thrombolysis, and patients without PPCI were excluded. Data collected included the number of subjects, patient characteristics, number of interventions in each group, methodological quality of the study, outcome of the method examined, and the length of follow-up. Outcomes evaluated included MI, stent thrombosis, all-cause mortality, and stroke. Cochrane's risk of bias tool was employed to evaluate the danger of bias in each investigation.¹⁰ Statistical analysis was performed based on the Cochrane Collaboration and PRISMA guidelines.⁸ Meta-analyses was done employing Review Manager (RevMan) 5.1. Chi-square test of heterogeneity and measures of trial inconsistency (I^2) data of incongruence were employed to evaluate heterogeneity between the studies. I^2 numbers of 25%, 50%, and 75% correspond to low, medium, and elevated heterogeneity. Combined estimate values of odd risks (ORs) with their 95% confidence intervals (CIs) were worked out applying the Mantel-Haenszel method. It was believed that values in the report were two-tailed, and hypothesis-checking outcomes had a statistical significance benchmark of $p < 0.05$. The small study impact, involving publication bias, was checked employing funnel plot, the Begg's log-rank test and the Egger's test.

Results

Initially, 848 studies were located from among whom 107(12.6%) duplicates were eliminated. Of the remaining, 709(95.7%) papers were excluded for being irrelevant. The remaining 32(4.3%) papers with full text were evaluated for suitability, and 30(93.75%) of them were discarded as they were meta-analysis, commentary, or letter to editors; or unfavourable clinical results were not presented in their endpoints. The final sample had 2(0.23%) studies (Figure 1).

Of the 2 studies 1(50%) was an RCT and 1(50%) was a prospective cohort study, and , based on quality

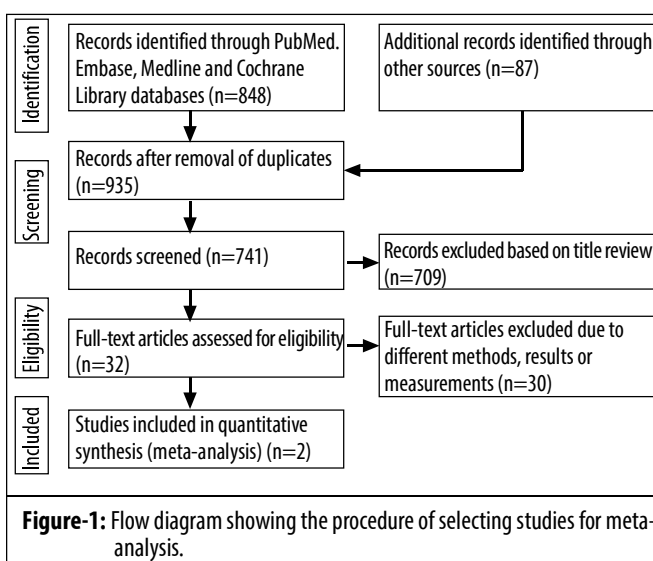


Table-1: Baseline characteristics of randomised studies.

Randomised studies	Year	Sample size (group) Pre-Treatment	Control	Inclusion criteria	Exclusion criteria	Endpoints	Mean follow-up period
TLANTIC ¹⁵	2016	799	830	Diagnosis of STEMI of between 30 min and 6 h with expected time from the qualifying electrocardiogram to first balloon inflation of <120 min. All patients then received maintenance treatment with 90 mg ticagrelor twice daily for at least 30 days to a maximum of 12 months	Did not undergo primary PCI.	death, new MI, urgent revascularization, definite stent thrombosis, or bail-out glycoprotein IIb/IIIa inhibitor use	24 hours
Alessandro et al. ¹⁶	2016	143	143	Acute coronary syndrome presenting with ST-segment elevation (STE-ACS) patients undergoing primary PCI, taking into account clinical presentation, electrocardiographic findings and the results of serum biochemical markers of necrosis. Patients were treated according to usual clinical practice and PCI was performed using standard techniques.	Patients younger than 18 years, patients presenting more than 12 h after onset of symptoms onset, patients treated with thrombolysis, patients in which primary PCI had failed to mechanically restore the patency of the culprit coronary vessel, and patients unable to provide informed consent.	Thrombolysis in myocardial infarction (TIMI) flow grade in the infarct related coronary artery (IRCA) before primary PCI, the clinical and angiographic pre- and post-procedural outcomes and the rates of in-hospital major adverse cardiovascular events and definite stent thrombosis.	48 hours

Table-2: Patient characteristics in each randomised trial.

Demographics	Atlantic		Alessandro et al.	
	Pre-treatment Group	Control Group	Pre-treatment Group	Control Group
Age, mean	69.9	69.9	64.0	64.4
Male sex (n)	649		671	109 108
Anterior MI (n)	361	417	70	70
Inferior/unknown MI (n)	483	413	73	73
Symptoms to PCl (min)	157	161	240	258.6
Diabetes mellitus (n)	98	116	24	34

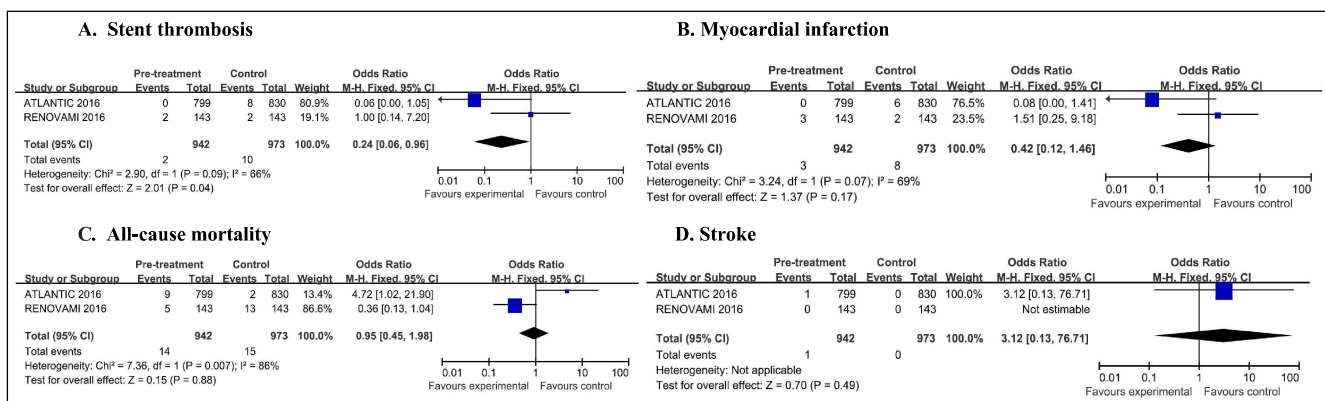


Figure-2: A: Fixed-effect meta-analysis for stent thrombosis. The figure shows the number of events, number of patients in the pre-treatment group and control group, odds ratio (OR), and 95% confidence interval (CI) for each trial, overall OR estimate with 95% CI and *p*-value for association test, *p*-value for heterogeneity test, and (I²) measures of trial inconsistency. B: Fixed-effect meta-analysis for myocardial infarction. C: Fixed-effect meta-analysis for all-cause mortality. D: Fixed-effect meta-analysis for stroke.

evaluation, the 2 studies were deemed to be at low risk of bias (Table 1).

The studies together had 1915 patients; 942(%) in the pre-treatment group, and 973(%) in the control group (Table 2). The rate of stent thrombosis in the control group was higher than in the pre-treatment group (*p*<0.01), but there were no significant differences in all-cause mortality (*p*=0.88), myocardial infarction (*p*=0.17) and stroke (*p*=0.49) (Figures 2A-D).

Discussion

PPCI is an effective method for patients suffering from STEMI.¹¹ It involves a lower risk of myocardial injury because the infarcted arteries are reperfused promptly. This may reduce the mortality rate and improve the quality of life. STEMI patients benefit from a good pre-treatment before PPCI.¹² The mainstream view is that pre-hospital ticagrelor treatment can reduce the incidence of thrombus burden and new MI in STEMI patients undergoing PPCI, but it results in significantly increased all-cause mortality.^{5,13} One of the studies in this meta-analysis was found to have a few limitations. For example, it did not seem very likely that there would be a different point of

only 31 min between the pre-admission and in-hospital ticagrelor groups.¹⁴ We integrated the relevant research through comprehensive and systematic searching. We performed a meta-analysis to draw a relatively comprehensive clinical conclusion. Although one study was a non-RCT, it showed little correlation bias (such as attrition bias, selective bias, etc.). We observed no dramatic difference among Egger's test results concerning patients' results analysed, and the funnel chart analysis demonstrated symmetry conforming to publication bias. The current meta-analysis ascertained that pre-hospital and in-hospital ticagrelor with respect to stent thrombosis in PPCI were significantly different. The pre-hospital groups were found to have significantly reduced the incidence of stent thrombosis. The most important discovery made in this meta-analysis is that all-cause mortality between the groups was not statistically significant. Although only two studies were involved in this meta-analysis,^{15,16} they showed very different results, which has significance for clinical practice. The pre-hospital ticagrelor group had significantly increased all-cause mortality in one study, but the other showed the pre-hospital ticagrelor group to have reduced all-cause mortality.^{15,16} The major factor

might be the time interval between the groups: the impact of pre-admission ticagrelor may have been observed only after PPCI because there was only 31 min in the Atlantic study, and the other study showed at least 1.5 hours before PPCI between the groups.^{15,16} The two studies showed pronounced heterogeneity, but the source of heterogeneity would not affect the final conclusion. With regard to the number of cases in the two studies, we are of the opinion that one should not necessarily be given more weight over the other.^{15,16}

Finally, our findings showed that all-cause mortality between pre-hospital and in-hospital ticagrelor treatment among patients suffering from STEMI was not statistically significant. Stent thrombosis was significantly different, and pre-hospital ticagrelor could significantly decrease the morbidity of stent thrombosis. The morbidity of new MI between the groups was significantly different. However, no analytical significance can be associated to the findings because of its low incidence. The results provide credible and academically valuable information. The current study does have some limitations. Firstly, only one RCT was found to have focussed on the topic, and we had to extract data from observational studies, leading to innate bias, particularly in terms of design, choice, therapy, and publication. Moreover, instead of rates of single-patient data, we based our conclusions on published event rates. As such, confounding and selection bias could not be ruled out in these studies, and some clinical results may have been influenced by some amount of inter-study heterogeneity. Lastly, there was no way for the analysis to study the particular method of PCI. Despite the limitations, however, there were three factors to overcome the constraints. First, the inclusion and exclusion criteria in the two studies were closely consistent. Second, the patients of the second study had been selected via a randomised approach similar to that in the first study.^{15,16} Third, the main difference between the two studies was the time interval between pre-hospital and in-hospital groups, and this difference had a significant effect on the results.

Conclusion

Pre-hospital ticagrelor did not increase all-cause mortality or the morbidity of new MI, but it did lower the risk of stent thrombosis for patients suffering STEMI undergoing PPCI.

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Conflict of Interest: None.

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