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Role of ticagrelor in the peri-thrombolytic phase for patients with ST-segment elevation myocardial infarction: a comprehensive review

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Abstract
Recent years have seen ticagrelor, a potent P2Y12 inhibitor, emerge as a significant advancement in the peri-thrombolytic management of patients with ST-segment elevation myocardial infarction (STEMI), offering a promising alternative to traditional antiplatelet drugs like clopidogrel. This review critically examines the efficacy and safety of ticagrelor during the peri-thrombolytic phase in STEMI patients, drawing on evidence from key clinical trials such as TREAT and MIRTOS, as well as other relevant studies. These investigations underscore ticagrelor's superior platelet inhibition capabilities, which are crucial for minimizing thrombotic complications post-thrombolysis without increasing bleeding risks. Despite its potential, clopidogrel remains the guideline-recommended choice for such patients, leaving the appropriateness of ticagrelor in this context open to debate. By summarizing the current evidence and identifying gaps in our understanding, this study advocates for targeted research to clarify the long-term benefits and optimal deployment of ticagrelor, highlighting its evolving significance in cardiovascular care.

Keywords STEMI, Thrombolytic therapy, Clopidogrel, Ticagrelor

Introduction

Coronary artery disease (CAD) remains a leading cause of mortality globally, with ST-segment elevation myocardial infarction (STEMI) representing its most acute and life-threatening manifestation [1]. Despite advances in reperfusion strategies, the optimal management of STEMI, particularly in settings where primary percutaneous coronary intervention (PCI) is not immediately available, continues to be a significant clinical challenge. Thrombolytic therapy offers a vital alternative in such scenarios, but the accompanying risk of thrombosis necessitates effective adjunctive antiplatelet therapy [2]. This review explores the role of ticagrelor, a potent P2Y12 inhibitor, in the peri-thrombolytic phase of STEMI treatment. By examining recent clinical trials and guidelines, we aim to assess ticagrelor's efficacy and safety compared to traditional therapies, such as clopidogrel, and discuss its potential implications for improving clinical outcomes in STEMI patients.

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Search strategy

The literature search focused on key topics including STEMI, thrombolytic therapy, pharmaco-invasive strategies, clopidogrel, ticagrelor, P2Y12 antagonists, et al. We included a variety of study types such as clinical guidelines, randomized controlled trials, observational studies, meta-analyses, et al. The search was conducted from inception up to June 2024 to ensure a comprehensive review of relevant literature.

Pharmaco-invasive therapy for STEMI patients in contemporary clinical practice

CAD is currently one of the leading causes of death and increased health care costs worldwide, and STEMI is the most urgent manifestation and has a high morbidity and mortality rate [3]. When primary PCI (PPCI) can be performed within 120 min by an experienced team, it is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset [4]. However, Large majority of patients with STEMI who present to non-PCI facilities cannot subsequently receive PPCI within guideline recommended times. In this case, pharmaco-invasive therapy is indicated as the reperfusion modality of choice, in the absence of contraindications [5]. In 2002, As the pioneer of pharmaco-invasive therapy, Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study first demonstrated that within 30 days, the incidence of cardiogenic shock and mortality rates were lower in the pharmaco-invasive therapy group compared to the group transfer for PPCI [6, 7]. Similar conclusions were drawn from a 5-year follow-up of the study, indicating that the mortality rate in the pharmaco-invasive group remained lower than that transfer for PPCI [8]. Subsequently, the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial found that a strategic alignment of prehospital or early fibrinolysis and contemporary antithrombotic co-therapy coupled with timely coronary angiography resulted in effective reperfusion as PPCI in patients with STEMI who presented within 3 h after symptom onset and who could not undergo PCI within 1 h after the first medical contact [9].

However, full-dose Tenecteplase in older patients is associated with increased intracranial hemorrhage risk in STREAM [9]. Several studies have begun to explore the feasibility of a half-dose thrombolytic regimen. The EARLY-MYO trial indicated that a pharmaco-invasive strategy utilizing half-dose Alteplase not only achieved equivalence with PPCI in terms of efficacy and safety but also resulted in superior epicardial and myocardial reperfusion in STEMI patients with anticipated delays in PPCI [10]. The STREAM-2 study also reached a similar conclusion, suggesting that a half-dose thrombolytic regimen may be feasible for patients over 60 years of age [11]. Therefore, half-dose thrombolysis may be a suitable option for specific populations.

With the swift progress in PCI, newer cardiologists are becoming less acquainted with the use of thrombolytic therapy, opting to use it sparingly in their clinical practice [12]. The success of the PPCI approach is largely contingent on the promptness of its administration. However, data from various registries and practical observations indicate that the time to ischemia often surpasses the recommended durations, particularly in densely populated urban centers [13]. This delay is notably critical as it contributes to increased morbidity and mortality rates, especially among patients with larger areas of myocardial infarction. To counteract these delays, there have been efforts to minimize time to treatment by adopting a facilitated PCI approach, which involves administering fibrinolytic therapy followed by a swift transfer for PCI, ideally within 90 to 120 min. While this approach has shown to improve the flow grade in the artery responsible for the infarction and enhance microcirculatory perfusion compared to traditional PPCI, it has also been associated with a higher risk of bleeding, particularly intracranial hemorrhage. This increased risk may be linked to the routine administration of glycoprotein IIb/IIIa inhibitors to all patients and the prevalent use of femoral access points. The current standing of the facilitated PCI strategy, in terms of efficacy and safety, remains ambiguous. The results from the ongoing OPTIMAL-REPERFUSION trial (NCT04752345) are anticipated to provide critical insights into this approach [14].

In conclusion, timely PPCI remains the gold standard for reperfusion therapy in treating STEMI as per current medical guidelines. Yet, the reality of frequent delays underscores the significance of adopting pharmaco-invasive tactics (Fig. 1). Present research is primarily aimed at refining this strategy to improve outcomes in STEMI management. This includes exploring the use of advanced thrombolytic agents, employing lower doses of thrombolytics, and adapting the facilitated PCI technique within the framework of innovative treatment methodologies.

Antiplatelet strategies in STEMI thrombolysis

Due to the central role of platelets in the pathophysiology of arterial thrombosis, dual antiplatelet therapy (DAPT) typically aspirin combined with an P2Y12 inhibitor is the cornerstone of STEMI patient management and is recommended, regardless of the reperfusion treatment modality.

Previous studies have shown that fibrinolysis itself may induce a prothrombotic state with high platelet reactivity (HPR) through enhanced platelet activation [15–17]. Specifically, thrombolytic drugs may increase the exposure of unstable atherosclerotic plaque ruptures and damaged endothelium, promoting platelet activation and

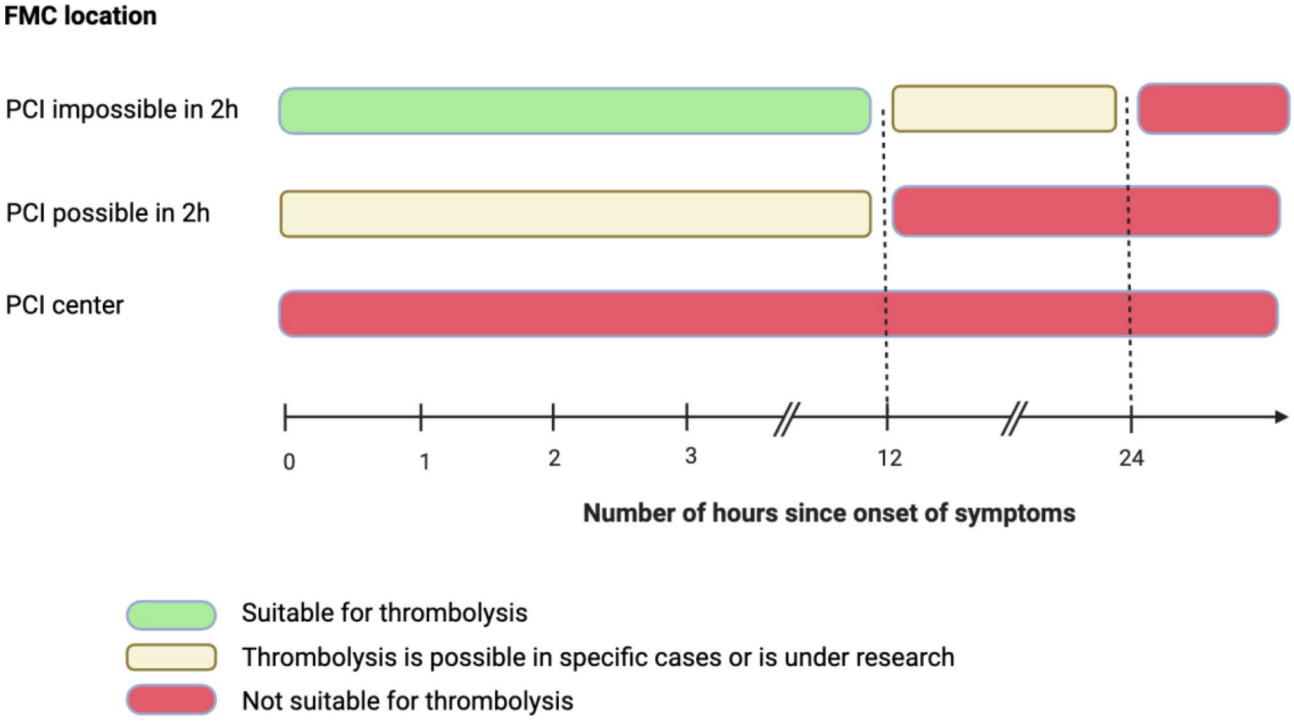

Fig. 1 Current indication of thrombolytic therapy in patients with STEMI. PCI, percutaneous coronary intervention. STEMI, ST-segment elevation myocardial infarction

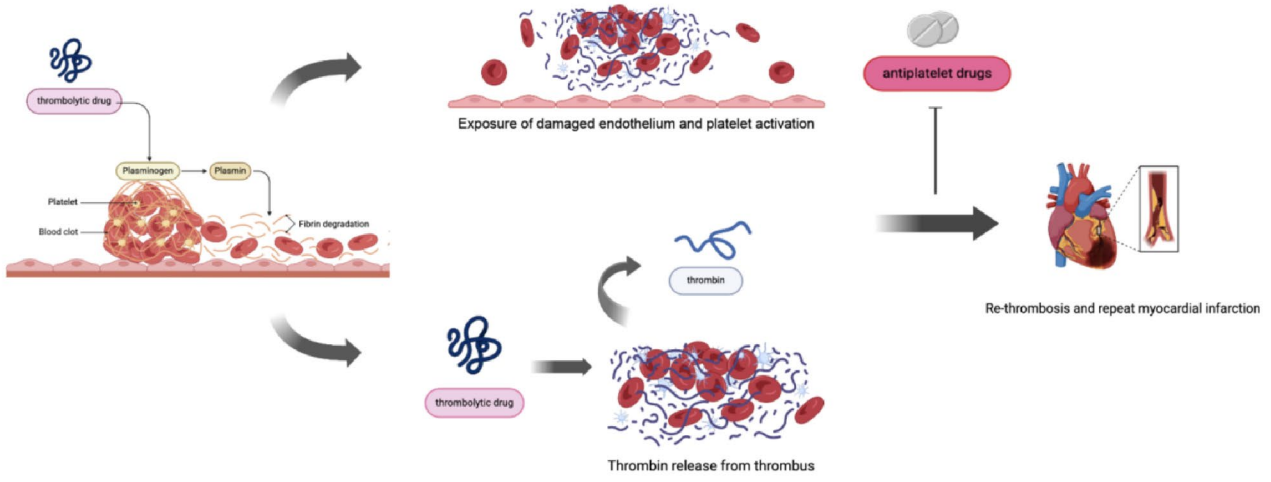

Fig. 2 Major mechanisms of re-thrombosis after thrombolytic therapy in patients with STEMI. STEMI, ST-segment elevation myocardial infarction

aggregation and making thrombus formation more likely in the short term, meanwhile thrombolytic drugs themselves have procoagulant effects, which may result in the release of thrombin from the thrombus, leading to the formation of thrombus (Fig. 2) [18–20].

Initially, in the ISIS-2 (Second International Study of Infarct Survival) trial, 150 mg of aspirin in combination with streptokinase for thrombolysis in patients with STEMI resulted in a 35-d reduction in mortality without an increase in bleeding compared with streptokinase alone [21]. Subsequent studies have begun to demonstrate the advantages of aspirin combined with clopidogrel in the peri-thrombolytic period. The CLARITY-TIMI 28 study [2] included 3,491 patients with STEMI who had received thrombolytic therapy and were treated with clopidogrel (300 mg loading dose, 75 mg/d maintenance) in combination with aspirin or aspirin monotherapy. The results of the study showed that the

primary efficacy endpoint (composite endpoint of arterial occlusion, death and recurrent myocardial infarction before angiography) was significantly lower in the clopidogrel combination group than in the single-agent group (15.0% versus 21.7%, $P<0.001$), and that the 30-d composite endpoint of death from cardiovascular causes, recurrent myocardial infarction, or recurrent ischemia leading to the need for urgent revascularization was approximately 20% lower in the clopidogrel combination group ($P=0.03$). The COMMIT/CCS2 trial study showed similar results, with the clopidogrel group (75 mg/d) reducing the relative risk of death, myocardial infarction, and stroke by 8.9% over 28 d compared with the placebo group on the basis of aspirin and other standard therapies (9.2% versus 10.1%, $P=0.002$) [22] .

Due to the benefits of DAPT in the peri-thrombolytic period as demonstrated in the above studies, current guidelines recommend that DAPT should be initiated as early as possible (prior to thrombolysis) in all patients with STEMI [1, 23].

Due to the use of aspirin in combination with clopidogrel as part of the DAPT regimen in previous studies, such as CLARITY-TIMI 28 [2] and COMMIT/CCS2 [22], both the 2017 ESC DAPT guideline [23] and the 2023 ESC ACS guideline [1] recommend this combination as an antiplatelet strategy during the peri-thrombolytic period.

Several compelling factors contribute to the prevalent preference for clopidogrel over ticagrelor during the critical peri-thrombolysis period. Primarily, cost considerations play a significant role; ticagrelor is generally associated with a higher cost, which can substantially influence the prescribing decisions of hospitals and clinicians, particularly in resource-limited healthcare settings. Furthermore, ticagrelor has been associated with an increased incidence of adverse effects compared to clopidogrel, notably in relation to dyspnea and bleeding risks. These potential complications may lead some clinicians to reconsider their choices, thereby favoring clopidogrel for specific patient populations. Additionally, clopidogrel has a longer history of clinical use, which cultivates a sense of familiarity and confidence among healthcare providers regarding its efficacy and safety. For many practitioners, the appeal of a more conservative and well-established treatment option often represents a safer choice.

The promising role of ticagrelor in the peri-thrombolytic phase

In comparison to thienopyridine drugs such as clopidogrel, ticagrelor exhibits a faster, stronger, and more consistent platelet inhibition effect, which is of significant importance for STEMI patients [24, 25]. Since the PLATO study, ticagrelor has gradually become the preferred P2Y12 antagonist for patients with ACS [26]. The subgroup analysis of PLATO study's STEMI subgroup of 8,430 patients showed that ticagrelor significantly reduced the risk of cardiovascular events compared to clopidogrel (9.3% vs. 11.0%, $P=0.02$) [27]. However, while the PLATO study demonstrated the superiority of ticagrelor in STEMI, it excluded patients who had undergone thrombolysis within 24 h prior to randomization, thereby limiting the generalizability of its conclusions to the thrombolysis population.

The TREAT study [28] aimed to fill a significant gap in our understanding by focusing on patients with STEMI who experienced symptoms within the past 24 h and underwent fibrinolytic therapy, with a notable 89.4% also receiving clopidogrel. These patients were then assigned randomly to either continue with clopidogrel or switch to ticagrelor treatment (the median duration from fibrinolysis to randomization was 11.5 h). Although the study indicated that ticagrelor after fibrinolytic therapy did not significantly reduce the frequency of cardiovascular events compared to clopidogrel, the findings suggested that ticagrelor was comparably safe to clopidogrel, as assessed by the primary safety endpoint of the first major bleeding event defined by the Thrombolysis In Myocardial Infarction (TIMI) criteria. Then, the MIRTOS trial [29], enrolling 335 STEMI patients under 75 eligible for thrombolysis, found no significant difference in Corrected TIMI Frame Count (CTFC) between clopidogrel and ticagrelor groups (24.33 ± 17.35 vs. 28.33 ± 17.59, $P=0.10$). Similarly, the risk of MACE was comparable across groups. These studies collectively bolster our confidence in employing ticagrelor during the peri-thrombolytic phase in patients with STEMI.

In fact, for many years, cardiologists have unanimously believed that clopidogrel, a relatively milder P2Y12 inhibitor, should be chosen during the peri-fibrinolytic phase of STEMI due to the increased risk of major bleeding, associated with ticagrelor in most relative studies [26]. Some experts have even subjectively considered recent use of ticagrelor prior to thrombolysis as a contraindication to fibrinolytic therapy. However, with the publication of the MIRTOS study, concerns regarding the safety of using ticagrelor prior to thrombolysis in STEMI patients have been alleviated, as ticagrelor was not found to increase the risk of major bleeding in these patients [29]. Furthermore, the research conducted by Dehghan et al. [30] involved 140 STEMI patients who received fibrinolytic therapy with Tenecteplase, who were randomly assigned to either clopidogrel or ticagrelor groups before PCI procedure. The findings of this study highlighted a significant difference in platelet reactivity between the two groups. Specifically, in the clopidogrel group, about 80% of patients transferred for early PCI exhibited elevated levels of residual platelet reactivity. In contrast, all

patients in the ticagrelor group demonstrated platelet reactivity unit (PRU) of 208 or less, indicating a more uniform and effective inhibition of platelet aggregation. In another trial, Alexopoulos et al. [20] augmented the loading dose of clopidogrel to 600 mg, yet the results continued to favor ticagrelor. Specifically, they observed that the HPR rates at 2- and 24-hours post-administration were significantly lower in the ticagrelor group compared to the clopidogrel group (14.3% vs. 82.1%, $p<0.001$, and 0% vs. 25.0%, $p=0.01$, respectively). This evidence reinforces the superior efficacy of ticagrelor in reducing platelet reactivity when compared to even a higher loading dose of clopidogrel.

In summary, current trial outcomes mark a significant step forward in identifying optimal antiplatelet therapy during the peri-thrombolytic phase for STEMI patients (Table 1), suggesting ticagrelor as a feasible option during the peri-fibrinolytic period.

Choice of P2Y12 agents in the "Overlooked" pre-thrombolysis phase

In fact, the 2017 ESC STEMI guidelines [5] and the 2023 ESC ACS guidelines [1] do not provide specific recommendations regarding the type of P2Y12 inhibitor to be used as a loading dose prior to thrombolysis in STEMI patients, primarily due to the scarcity of pre-thrombolysis studies (Table 2). However, post-thrombolysis antiplatelet therapy has received a class IA recommendation for clopidogrel, mainly because previous studies have demonstrated that the combination of aspirin and clopidogrel post-thrombolysis offers greater benefits to patients compared to aspirin alone [1, 5]. There have been no direct comparative studies among different types of P2Y12 inhibitors in this context. Therefore, this field still lacks substantial evidence-based medicine to determine the optimal peri-thrombolytic antiplatelet regimen.

In the TREAT study [28], ticagrelor was administered on average 11.4 h after thrombolysis, with 90% of the subjects having been pretreated with clopidogrel prior to thrombolysis. Consequently, the TREAT study does not address the question of whether ticagrelor can be used before thrombolysis. Thus, to date, only one study, the MIRTOS study [29], has demonstrated the feasibility of administering ticagrelor prior to thrombolysis using clinical endpoints (Fig. 3).

However, the primary focus of the MIRTOS study was not on clinical outcomes, and the follow-up period was too short to conclusively prove that pre-thrombolysis administration of ticagrelor can improve long-term patient prognosis [29]. Although ticagrelor administered in pre-thrombolysis demonstrated more effective inhibition of platelet aggregation, given that biological assay results and clinical outcomes do not always align, further research is needed to assess the safety and efficacy of ticagrelor used before thrombolysis. Notably, the incidence of MACE and major bleeding events in MIRTOS did not differ significantly between the two groups. This finding could alleviate concerns about the potential for increased bleeding risk with ticagrelor loading prior to thrombolysis, potentially leading to changes in clinical guidelines.

Additionally, it is noteworthy that the ISAR-REACT 5 study found that among patients presenting with ACS, with or without ST-segment elevation, the incidence of death, MI, or stroke was significantly lower in those who received prasugrel compared to those who received ticagrelor, while the incidence of major bleeding did not differ significantly between the two groups [32]. We speculate that prasugrel may also be well-suited for the peri-procedural period of STEMI; however, this hypothesis requires further clinical research evidence for support.

Conclusion and clinical perspectives

This comprehensive review highlights the nuanced role of ticagrelor in the peri-thrombolytic phase for STEMI patients, emphasizing its potent compared to traditional thienopyridines like clopidogrel. Clinical trials such as TREAT and MIRTOS demonstrate that ticagrelor is a safe and effective alternative in this setting, challenging previous norms and suggesting its broader inclusion in clinical guidelines. However, the complexity of patient profiles and thrombolytic timing necessitates a personalized approach to antiplatelet therapy, with further research needed to establish the long-term benefits and risks of pre-thrombolysis ticagrelor use. As the landscape of antiplatelet therapy in STEMI management evolves, ongoing evaluation of new data will be essential to optimize patient outcomes in this critical area of cardiovascular care.

Table 1 Major study comparing efficacy and safety of ticagrelor and clopidogrel in patients with STEMI undergoing thrombolysis therapy

Study	Sample Size	Population	Fibrinolytic drug	Randomized time	P2Y12 dosing	Follow up	Primary Outcome	Conclusion	Reference
TREAT	3799	STEMI patients < 75 years old presented within 24 h of the onset of symptoms and received fibrinolytic therapy		A median of 11.4 h (IQR: 5.8 to 18.1 h) after fibrinolytic therapy	Ticagrelor with a loading dose of 180 mg or clopidogrel with a loading dose of 300 to 600 mg	12 months	Death from vascular causes, MI, stroke, severe recurrent ischemia, TIA, or other arterial thrombotic event	Among patients age < 75 years with STEMI, administration of ticagrelor after fibrinolytic therapy did not significantly reduce the frequency of cardiovascular events when compared with clopidogrel.	[28]
MIRTOS	335	Patients < 75 years old with STEMI eligible for thrombolysis	73% Tenecteplase,26–27% Reteplase, 0–1% Alteplase	Immediately before thrombolysis.	Clopidogrel group patients received a 300 mg loading dose and a 75 mg maintenance dose, and ticagrelor group patients received a 180 mg loading dose and a 90 mg bid maintenance dose.	3 months	CTFC	Thrombolysis with ticagrelor in patients < 75 years old was not able to demonstrate superiority compared to clopidogrel in terms of microvascular injury, while there was no difference between the two groups in MACE and major bleeding events.	[29]
Alexopoulos et al.	56	Patients with STEMI having undergone thrombolysis in the previous 3–48 h in a non PCI-capable hospital, had platelet function assessment on admission to the PCI-capable hospital and prior to coronary angiography	83.1% tenecteplace, 16.9% reteplace	After Hour 0 (platelet function testing for the first time)	Ticagrelor 180 mg LD, followed by 90 mg bid MD starting 12 ± 6 h post LD, until discharge or clopidogrel 600 mg LD, followed by 150 mg od MD starting 12 ± 6 h post LD, until discharge.	Pre-discharge	Platelet reactivity at Hour 2 post randomization	Ticagrelor treats HPR more effectively compared to high dose clopidogrel therapy.	[20]

Table 1 (continued)

Study	Sample Size	Population	Fibrinolytic drug	Randomized time	P2Y12 dosing	Follow up	Primary Outcome	Conclusion	Reference
Dehghani et al.	140	Patients undergoing PCI within 24 h of Tenecteplase, aspirin, and clopidogrel for STEMI。	Tenecteplase	At the time of diagnostic angiogram and immediately went on to receive the loading dose of their assigned anti-platelet prior to PCI.	Ticagrelor 180 mg LD followed by 90 mg BID or clopidogrel 300 mg LD followed by 75 mg daily	1 month	platelet reactivity units ≤ 208 at 4 h.	In patients managed with a pharmacoinvasive approach for STEMI, ticagrelor administered prior to PCI was superior to clopidogrel in achieving therapeutic platelet inhibition.	[30]
Yang et al.	212	undergoing PCI within 24 h of TNK, aspirin, and clopidogrel for STEMI	Tenecteplase	At the time of diagnostic angiogram and immediately received a loading dose of their assigned anti-platelet prior to PCI after baseline PRU had been drawn.	Ticagrelor 180 mg LD followed by 90 mg BID or Clopidogrel 300 mg LD followed by 75 mg daily	1–12 month	PRU at follow-up beyond 24 h based on drug randomization	In patients undergoing PCI within 24 h of fibrinolysis for STEMI, Ticagrelor provides prolonged platelet inhibition compared with Clopidogrel.	[31]

STEMI, ST-segment elevation myocardial infarction; TNK, Tenecteplase; PCI, percutaneous coronary intervention; LD, loading dose; PRU, platelet reactivity unit; HPR, high platelet reactivity; MD, maintenance dose; CTFC, corrected TIMI frame count; IQR, interquartile range; MI, myocardial infarction; MACE, major adverse cardiovascular events

Table 2 Guideline recommendations and recent studies on P2Y12 inhibitor selection in pre-thrombolysis and post-thrombolysis phases

Time	ESC Guideline Recommendation for P2Y12 Inhibitor Selection	Reasons for Guideline Recommendation	Recent Related Studies
Pre-thrombolysis	No recommendation	Lack of relevant studies	• MIRTOS: Ticagrelor is comparable to clopidogrel in terms of both CTFC and MACE[29] • Alexopoulos et al.: Ticagrelor treats HPR more effectively [20] • Dehghani et al.: Ticagrelor superior to clopidogrel in achieving therapeutic platelet inhibition [30]
Post-thrombolysis	Clopidogrel is recommended as Class IA, while ticagrelor is not recommended	There are only studies using clopidogrel, with a lack of studies on ticagrelor	• TREAT: Ticagrelor is comparable to clopidogrel in terms of MACE [28] • Yang et al.: Ticagrelor provides prolonged platelet inhibition compared with clopidogrel [31]

CTFC, corrected TIMI frame count; HPR, high platelet reactivity; MACE, main adverse cardic events

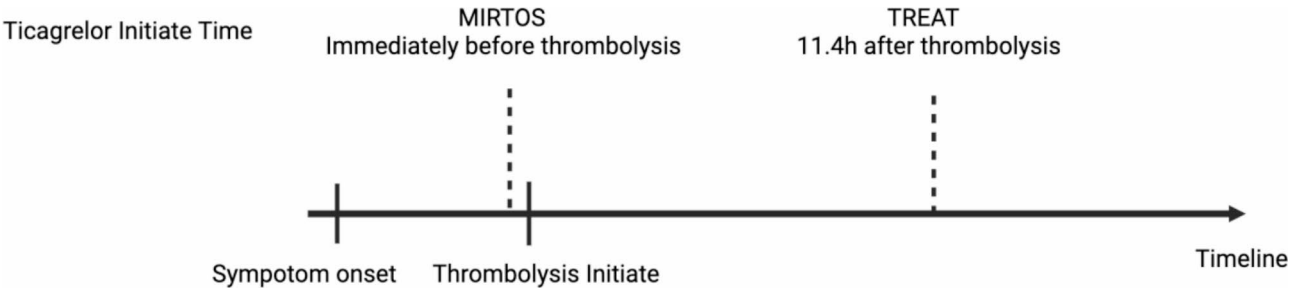

Fig. 3 Initiation time of ticagrelor in the MIRTOS study and the TREAT study

Abbreviations

STEMI	ST-segment elevation myocardial infarction
CAD	Coronary artery disease
DAPT	Dual-antiplatelet therapy
PCI	Percutaneous coronary intervention
STREAM	Strategic Reperfusion Early After Myocardial Infarction
FMC	First medical contact
PRU	Platelet reactivity units
CTFC	Corrected TIMI Frame Count
LD	Loading dose
TNK	Tenecteplase

Author contributions

J.Z. and L.L. conceived and designed the study. J.Z. and L.L. drafted the manuscript, and Z.C. and Y.H. substantively revised it for important intellectual content. All authors (J.Z., L.L., Z.C., and Y.H.) have approved the submitted version and any substantially modified version that involves their contribution to the study. Additionally, all authors have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated, resolved, and documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare no competing interests.

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