

Ticagrelor after Fibrinolytic: Is it Time to Consider?

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Worldwide, ischemic heart disease is the most common cause of death and its frequency is increasing. World Health Organization (WHO) in 2011 reported acute myocardial infarction as the leading cause of death in Indonesia with incidence rate 200 events per 100 thousand populations per year. ST-segment elevation myocardial infarction or STEMI is a form of ischemic heart disease with the highest mortality rate.¹

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Several recent studies have highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention.² Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 hour of symptoms onset, provided it can be performed expeditiously (120 min from STEMI diagnosis) by an experienced team. However, in some circumstances, primary PCI is not an immediate option and fibrinolysis could be initiated expeditiously.²

Based on iSTEMI publication, patients awareness time and patient transfer time in Indonesia require 3 hours or more. STEMI guidelines in US stated that ideal FMC-to-device time is 90 minutes or less in PCI-able hospital or 120 minutes in non-PCI-able hospital. iSTEMI publication record median time for FMC-to-device is 250 minutes and this delay will cause patient unelligible to receive PCI thus until now, fibrinolysis still considered as main treatment for STEMI.¹

Fibrinolysis therapy usually combined with antiplatelet and anticoagulation co-therapy. The recommendation for antiplatelet is clopidogrel as addition to aspirin.² Based on the results of COMMIT and CLARITY trial, early clopidogrel therapy will prevent reinfarction and strokes and continued treatment after hospital discharge could lead to further gains.^{3,4}

Despite the proven clinical efficacy of these agents, residual morbidity and mortality remain substantial even in patients receiving dual antiplatelet therapy and a significant number of clopidogrel-treated patients continue to exhibit high residual platelet reactivity, which has been linked to increased risk of ischemic complications.

Unlike clopidogrel, ticagrelor is not influenced by CYP2C19 polymorphism. The higher prevalence of loss of CYP2C19 function polymorphism in Asian patients may favor ticagrelor compared with clopidogrel in terms of platelet inhibition and may be related to the observed reduction in ischemic events. The main concern regarding the use of ticagrelor in this scenario is related to the risk of major bleeding, especially intracranial or fatal bleeding.

Asian patients are believed to be susceptible to antithrombotic or fibrinolytic and to be associated with a higher bleeding risk during management of ischemic heart diseases and antithrombotic therapy. The lower body weight of Asian patients, fixed dose regimen of most antiplatelet drugs, and different genetic backgrounds may explain the potential for this increased bleeding risk. In addition to a high residual risk for ischemic events, aspirin and P2Y¹² ADP receptor antagonists also are associated with increased bleeding risk.⁵

In Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was compared with clopidogrel for prevention of cardiovascular events in 18,624 patients with an acute coronary syndrome, with or without ST-segment elevation.⁶ At 12 months, treatment with Ticagrelor as compared with Clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke (hazard ratio 0,84; 95% confidence interval [CI] 0,77 to 0,92; $p < 0,001$) without an increase in the rate of overall major bleeding (11,6% and 11,2%; $p = 0,43$).⁶ In a subgroup analysis based on PLATO study, patient with STEMI and planned primary PCI showed consistent results with those observed in the overall PLATO trial.⁷

Although ticagrelor has demonstrated pharmacodynamic and clinical superiority to clopidogrel in patients with ACS, there are currently no data available at that time for its safety and efficacy in patients presenting with STEMI and being managed with a pharmacoinvasive approach. Therefore SET-FAST study was conducted to compare the effects of

Ticagrelor and Clopidogrel on platelet reactivity in patients undergoing PCI within 24 hours of receiving fibrinolysis for STEMI. In this high-risk population, Ticagrelor provides more prompt and potent platelet inhibition compared with Clopidogrel without significant difference of major bleeding.⁸

Despite the superiority clinical outcomes PLATO trial, patients who received fibrinolytic therapy in the preceding 24 hours were excluded. The main concern regarding the use of Ticagrelor in this scenario is related to the risk of major bleeding, especially intracranial or fatal bleeding. Thus TREAT trial was conducted to evaluate the safety of Ticagrelor in this clinical setting.⁹ This multicenter, randomized, open-label with blinded end point adjudication trial, involving 3799 patients with STEMI receiving fibrinolytic therapy from 10 countries. The follow-up period is 30-day. Patients were randomly assigned to receive Ticagrelor or Clopidogrel as early as possible after the index event and not more than 24 hours after the event.⁹

At 30 days, TIMI major bleeding had occurred in 14 of 1913 patients (0,73%) receiving Ticagrelor and in 13 of 1886 patients (0,69%) receiving Clopidogrel (absolute difference 0,04%; 95% CI -0,49% to 0,58%; $p < 0,001$ for non-inferiority). Major bleeding defined by the PLATO criteria and by the Bleeding Academic Research Consortium (BARC) types 3 to 5 bleeding was similarly showed non-inferiority. The rates of fatal bleeding (0,16% vs 0,11%; $p = 0,67$) and intracranial bleeding (0,42% vs 0,37%; $p = 0,82$) were similar between the Ticagrelor and Clopidogrel groups, respectively. Minor and minimal bleeding were more common with Ticagrelor than with Clopidogrel. This study concluded that in patients younger than 75 years with STEMI, delayed administration of Ticagrelor after fibrinolytic therapy was noninferior to Clopidogrel for TIMI major bleeding at 30 days.⁹

TREAT study was not powered to assess efficacy outcomes, therefore the efficacy result must be interpreted as exploratory. This trial also not address treatment of patients older than 75 years, who were excluded.⁹

Several experts in cardiology in Indonesia have discussed the TREAT study design and its preliminary 30 days results in order to generate the rationale position of Ticagrelor in STEMI thrombolysis treatment which in-line with daily clinical practice in Indonesia. The

meeting concluded that PLATO study is the cornerstone of Ticagrelor efficacy in ACS patients and the TREAT study (30 days results) provides evidence that Ticagrelor is as safe as Clopidogrel in STEMI patients after treated with fibrinolytic. However, the final result of 1-year follow-up of this study is still waited.

ESC guideline in 2017 gives recommendations for reperfusion therapy which is a primary PCI strategy is recommended over fibrinolysis within induced timeframes, but if timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 hours of symptom onset in patients without contraindications. Clopidogrel is the P2Y₁₂ inhibitor of choice as co-adjuvant and after fibrinolysis, but 48 hours after fibrinolysis, switch to prasugrel or ticagrelor may be considered in patients who underwent PCI.²

Indonesian Heart Association (PERKI) 2018 guideline in ACS management also gives similar recommendations on STEMI management. Recommendations for fibrinolytic therapy mention that is indicated as an addition to aspirin. Although clopidogrel is a recommended P2Y₁₂ inhibitor in fibrinolytic therapy, this guideline also mention that switching to ticagrelor can be considered in patients who will undergo PCI treatment after fibrinolytic.¹⁰

Whether ticagrelor should replace clopidogrel upon initial presentation to hospital in those who will undergo fibrinolytic strategy depend on further research. Based on the TREAT study preliminary result on 30 days, the use of ticagrelor within 24 hours after fibrinolytic therapy in patient younger than 75 years old can be considered with comparable safety profile to clopidogrel. But the physicians should decide on a patient-by-patient basis as to whether its benefit outweighs the risk.

List of Abbreviations

BARC: Bleeding Academic Research Consortium
 PCI: Percutaneous Coronary Intervention
 STEMI: ST-segment elevation myocardial infarction
 WHO: World Health Organization

References

1. Kelompok Kerja Perhimpunan Dokter Spesialis Kardiovaskular. Pilot Program Jejaring Indonesia

2. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39:119-77.
3. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005; 352: 1179-89.
4. COMMIT collaborative group. Addition of clopidogrel to aspirin in 45852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005; 366: 1607-21.
5. Cohen, M. Oral Antiplatelet Therapy for Acute and Chronic Management of NSTEMI ACS: Residual Ischemic Risk and Opportunity for Improvement. *Cardiovasc Drugs Ther*. 2009; 23(6): 489-99.
6. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndrome. *N Engl J Med*. 2009;361:1045-57.
7. Steg PG, James S, Harrington RA, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndrome Intended for Reperfusion With Primary Percutaneous Coronary Intervention: A Platelet Inhibitor and Patient Outcomes (PLATO) Trial Subgroup Analysis. *Circulation*. 2010;122:2131-41.
8. Dehghani P, Lavoie A, Lavi S, et al. Effects of ticagrelor versus clopidogrel on platelet function in fibrinolytic-treated STEMI patients undergoing early PCI. *Am Heart J*. 2017;192:105-12.
9. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction. *JAMA Cardiol*. 2018;3(5):391-9.
10. Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI). Pedoman Tatalaksana Sindrom Koroner Akut. 4th edition. 2018.