

Optimization of Antiplatelet Therapy in STEMI

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Opinion statement

Antiplatelet therapy is an essential component of ST elevation myocardial infarction (STEMI) management. Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has previously been the standard of care for STEMI management, but the advent of newer, more potent P2Y12 inhibitors has expanded the options for the management of STEMI. As compared with clopidogrel, these newer P2Y12 agents—such as prasugrel and ticagrelor—allow for further reductions in ischemic end points, without the robust increases in bleeding seen in previous studies of antithrombotic therapies. Understanding the nuances of these newer agents allows optimization of therapy for the individual patient and circumstance. Ultimately, combining these newer therapies, in specific populations, and specific approaches—alternative access strategies (e.g., radial)—may allow us to maximize efficacy and reduce the risk of antiplatelet therapies in treating patients with STEMI.

Introduction

Platelets play a critical role in atherothrombosis and the pathogenesis of ST elevation myocardial infarction. As such, antiplatelet therapy is fundamental to STEMI management [1•]. A variety of platelet receptors have been exploited as therapeutic targets for STEMI in several randomized clinical trials (see Fig. 1). Optimizing antiplatelet strategies

requires maximizing reduction of ischemic events while minimizing major bleeding complications [2]. Understanding the properties of these newer agents, including options for delivery, may allow optimization of therapeutic strategies for the individual patient and circumstance. In this paper, we will review and update current options and the

supporting data and use updated data to consider intraprocedural, and post-procedural antiplatelet common questions around preprocedural, regimens for patients with STEMI.

Antiplatelet therapies

Aspirin

Aspirin (or acetylsalicylic acid) remains the cornerstone of antiplatelet therapy for STEMI. Aspirin indirectly inhibits thromboxane via its effects on the cyclooxygenase (COX) enzyme (Fig. 1). The benefits of aspirin in STEMI were first demonstrated in the Second International Study of Infarct Survival (ISIS-2), which studied 17,187 patients assigned to aspirin, intravenous streptokinase, both, or neither. After 5 weeks, patients treated with aspirin alone had a significant reduction in vascular mortality (23%), and this was additive with aspirin and streptokinase (42%) [3]. Most recently, aspirin dosing was studied in CURRENT-OASIS 7, which studied 25,086 patients with acute coronary syndrome (ACS) (29.2% with STEMI). After an initial load of ≥ 300 mg on day 1, the lower daily dose aspirin group (75–100 mg) did not have a difference in cardiovascular outcomes compared with the higher dose group (300–325 mg) and had less gastrointestinal bleeding [4].

Aspirin should be given as soon as the diagnosis of STEMI is considered, regardless of the treatment strategy. The standard of care in STEMI is to load with a higher dose of aspirin (162–325 mg) and then change to a lower daily dose (75–100 mg) [5••].

Choosing P2Y₁₂ receptor inhibitors

The ADP receptor (P2Y₁₂ receptor) initiates platelet aggregation and platelet activation when bound. It has become a critical target in management of myocardial infarction in general, and STEMI in particular. There are several agents (thienopyridines, cyclopentyl-triazolo-pyrimidine (CTP), ATP analog)

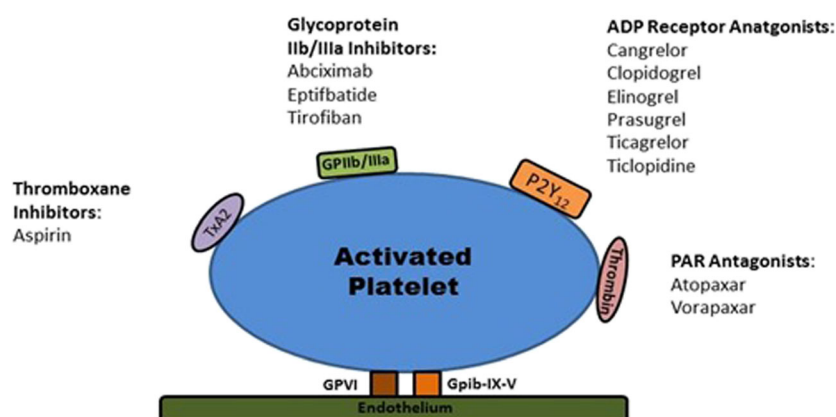


Fig. 1. Targets of antiplatelet therapy.

in this category (both oral and intravenous). Table 1 highlights important characteristics and differences.

Clopidogrel

Clopidogrel is a second-generation oral thienopyridine that irreversibly blocks the ADP receptor (P2Y₁₂ receptor) on platelets. It had largely replaced ticlopidine (a first-generation thienopyridine) because of improved safety profile while maintaining similar efficacy [6]. Clopidogrel use in STEMI was first evaluated in the CLARITY-TIMI 28 Study, which randomized 3491 patients with STEMI treated with a fibrinolytic agent and aspirin (150 to 325 mg loading, then 75 to 162 mg daily) to clopidogrel (300 mg loading, then 75 mg daily) or placebo [7]. Most patients underwent angiography (94%, generally at least 48 h after presentation), and among those patients, 57% had percutaneous coronary intervention (PCI) while 6% underwent coronary artery bypass grafting (CABG). The primary efficacy end point (a composite of an occluded infarct-related artery on angiography, death before angiography, recurrent myocardial infarction (MI) before angiography) was 21.7% in the placebo arm and 15% in the clopidogrel arm. At 30 days, clopidogrel reduced the composite end point (CV death, recurrent MI, recurrent ischemia needing PCI) by 20% (14.1 to 11.6%, $P = 0.03$). The rates of major bleeding and intracranial hemorrhage were similar in both groups. The COMMIT Study confirmed these findings among >45,000 patients predominantly with STEMI; dual antiplatelet therapy (DAPT) with clopidogrel reduced death, myocardial infarction, and stroke compared with aspirin alone (9.2 vs 10.1%, respectively, $P = 0.002$) [8].

After the clinical utility of DAPT with clopidogrel was established in these studies, later studies revealed variability in individual responses to clopidogrel and some of the limitations of its use. Suboptimal clopidogrel responses can be attributed to genetic factors, clinical factors (poor absorption, drug interactions), or cellular factors (upregulation of the P2Y₁₂ pathway) [9•]. As a pro-drug, clopidogrel requires hepatic metabolism for activation. Cytochrome P-450 polymorphism (carrier of the CYP2C19 allele) has been shown to have a 32.4% relative reduction of active metabolite of clopidogrel in plasma ($P < 0.001$) with an absolute reduction in platelet aggregation. Among the clopidogrel-treated patients in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38), carriers had a 53% higher composite outcome (CV death, MI, or stroke) compared with non-carriers (12.1 vs 8.0%, $P = 0.01$) [10]. These limitations of clopidogrel underlie the clinical need for more potent and reliable agents.

On the other hand, there are clinical scenarios in which less potent agents, such as clopidogrel, may have a more favorable risk-benefit profile. For example, patients on triple therapy requiring concomitant anticoagulation, elderly patients requiring dual-antiplatelet therapy, or other subpopulations with increased bleeding risk may be optimally served with aspirin and clopidogrel.

Prasugrel

Prasugrel is a third-generation oral thienopyridine and irreversible platelet P2Y₁₂ inhibitor, whose pharmacodynamic and pharmacokinetic properties yield a more potent, faster-acting, and more rapidly metabolized agent than

Table 1. P2Y₁₂ inhibitors and their characteristics

Agent	Class	Dose (loading/maintenance)	Time to peak onset	Reversibility (d/c before CABG)	Route/crushed	Contraindications
Ticlopidine	Thienopyridine (pro-drug)	500 mg/250 mg bid	48 h	No (5 days)	PO/?	Hematopoietic d/o severe liver disease
Clopidogrel	Thienopyridine (pro-drug)	600 mg/75 mg	6 h (600 mg) 12 h (300 mg)	No (5 days)	PO/yes	Active pathological bleeding (applies to all agents)
Prasugrel	Thienopyridine (pro-drug)	60 mg/10 mg	1–2 h	No (7 days)	PO/yes	Prior TIA/stroke, age ≥75 yo, wt <60 kg
Ticagrelor	Cyclopentyl-triazolo-pyrimidine (not a pro-drug)	180 mg/90 mg bid	1–2 h	Yes (2–5 days)	PO/yes	Hx of ICH (caution w/ severe COPD, gout, bradycardia)
Cangrelor	ATP analog (not a pro-drug)	4 µg/kg/min	3–6 min	Yes (1 h)	IV/(N/A)	Active bleeding (applies to all)

clopidogrel [11]. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38) established the drug's clinical efficacy and superiority, when it compared prasugrel with clopidogrel by enrolling 13,608 patients with acute coronary syndromes, including both NSTEMI-ACS as well as ST elevation MI [12].

Among those enrolled in TRITON, 3534 patients suffered from STEMI. The primary end point remained improved with prasugrel over clopidogrel at 15 months (10 vs 12.4%, HR 0.79, $P = 0.02$), with a significant reduction in both secondary end points (urgent TVR and stent thrombosis) [13]. There was no association with drug administration and timing of PCI (stratified by early (<12 h to PCI) and late (12 h to 14 days)). In the trial, the resultant lack of difference of non-coronary artery bypass grafting (CABG) TIMI bleeding (life-threatening, major, and minor) between prasugrel and clopidogrel seems remarkable, and this must be interpreted carefully, as these findings did not satisfy a formal test for interaction between the prasugrel- and clopidogrel-treated groups [14]. For those rare patients treated with CABG (4% of patients with STEMI were treated with bypass), CABG-related bleeding was significantly higher with prasugrel versus clopidogrel (18.8 vs 2.7%, OR 8.19, 95% CI 1.76–38.18, $P = 0.0033$). It is often recommended that prasugrel be held for 7 days prior to CABG.

However, it is important to note that in the main TRITON Study, the reported benefits came at the expense of significantly increased major bleeding (2.4 vs 1.8%, HR 1.32, 95% CI 1.03–1.68), life-threatening bleeds, and even fatal bleeds. In an important subsequent analysis of the main trial, the following groups fared worst, with no accrued clinical benefit from prasugrel: history of stroke or transient ischemic attack (TIA), age 75 years or greater, and weight 60 kg or less [12]. Those with stroke or TIA were harmed by prasugrel administration (HR 1.54, 95% CI 1.02–2.32), including increased intracranial hemorrhage (2.3% vs none on clopidogrel, $P = 0.02$).

Therefore, overall, prasugrel represents a more efficacious yet reasonably safe antiplatelet therapy in patients with STEMI treated with PCI compared with clopidogrel. This is reflected in the updated guidelines. Even in the setting of STEMI, history of stroke or TIA, age 75 years or greater, and weight 60 kg or less are considered relative contraindications to the use of prasugrel. At present, cost remains an issue for prasugrel and ticagrelor.

Ticagrelor

Ticagrelor is the first oral reversible P2Y₁₂ receptor inhibitor. It is not a thienopyridine but belongs to a chemical class called cyclopentyl-triazolopyrimidine (CPTP). It has rapid onset, and unlike clopidogrel and prasugrel, it does not require hepatic metabolism for its activity. Compared with clopidogrel, its inhibition of the P2Y₁₂ receptor is faster, stronger, and more consistent [15]. Ticagrelor was studied against clopidogrel in patients with acute coronary syndrome in the Platelet Inhibition and Patient Outcomes (PLATO) Study. Patients were randomized to either ticagrelor (180 mg loading, 90 mg bid maintenance) or clopidogrel (300 to 600 mg loading, 75 mg daily) [16•]. The results of the STEMI subgroup analysis of PLATO were overall consistent with the main trial. Of the 18,624 patients, 7544 patients were diagnosed with STEMI (or LBBB). The primary end point was reduced in ticagrelor vs

clopidogrel (9.4 vs 10.8%, $P = 0.07$). However, when an analysis was done to include patients who had a final diagnosis of STEMI (not just at presentation), the primary end point is reduced further with ticagrelor (9.3 vs 11.0%, $P = 0.02$) [17•]. Ticagrelor reduced several of the secondary end points in the STEMI population, including a composite of CV death and MI (8.4 vs 10.2%, $P = 0.01$). There was also a reduction in MI (4.7 vs 5.8%, $P = 0.03$), stent thrombosis ($P = 0.03$), and total mortality ($P = 0.05$).

In the main PLATO trial, there was an increase in non-CABG-related major bleeding (4.5 vs 3.8%, $P = 0.03$). In the STEMI subset, there was no difference in major bleeding ($P = 0.76$). The stroke rate (while low) was higher in the ticagrelor group (1.7 vs 1.0%, $P = 0.02$). Compared with the CURE trial and TRITON-TIMI 38 studies, the results of PLATO are notable because stronger platelet inhibition from ticagrelor did not result in increased bleeding. In addition, there was also a reduction in mortality seen in PLATO that was not observed in the other trials [18]. The new DAPT guidelines reflect a preference for ticagrelor over clopidogrel [5••].

Ticagrelor is known to have a variety of off-target effects, which may reflect endogenous adenosine levels from blocking the adenosine transporter ENT1 [19•]. The increased adenosine levels may explain some of the pharmacologic effects of ticagrelor such as increased incidence of dyspnea, decreased glomerular filtration, increased vasodilation, decreased reperfusion injury, and decreased electrical conduction. In PLATO, the ticagrelor group was noted to have increased dyspnea (13.8 vs 7.8%, $P < 0.001$), ventricular pauses (5.8 vs 3.6%, $P = 0.01$), and increased serum levels of uric acid and creatinine ($P < 0.001$). Despite the increased dyspnea, few in the study discontinued ticagrelor because of it (0.9%). However, discontinuation of ticagrelor due to adverse events was more frequent than that of clopidogrel (7.4 vs 6.0%, $P < 0.001$). The use of ticagrelor in patients with COPD is complicated. Some have suggested caution in using ticagrelor in patients with significant COPD—as well as moderate or severe renal failure, history of gout, or history of important bradycardia (without protection of a pacemaker) [18]. While COPD patients had a higher incidence of dyspnea with ticagrelor (26.1 vs 16.3%), the rate of discontinuation was still relatively low (ticagrelor 2.5% vs clopidogrel 0.9%), and a post hoc analysis of PLATO revealed that patients with COPD still had a lower primary end point with ticagrelor vs clopidogrel (14.8 vs 20.6%) [20].

Based on current data, ticagrelor seems preferable to clopidogrel in STEMI based on its efficacy and safety profiles in the STEMI subpopulation of PLATO. However, caution is advised in certain populations such as important bradycardia or severe COPD. In addition, patients must be able to comply with twice daily dosing, and as noted above, cost remains an issue for ticagrelor and prasugrel.

Cangrelor

Cangrelor is an ATP analog and an intravenous, direct-acting P2Y₁₂ receptor antagonist. It has a plasma half-life of 3 to 5 min with restoration of platelet function 1 h after stopping the infusion [21]. It has been studied in three large trials (CHAMPION PCI, CHAMPION PLATFORM, CHAMPION PHOENIX). The largest and most recent trial, CHAMPION PHOENIX, randomized 10,942 patients undergoing urgent or elective PCI to a cangrelor bolus and infusion or

clopidogrel loading dose (600 or 300 mg) [22]. Only a minority of these patients had STEMI on presentation (18.2%), though the effects seemed consistent in this subpopulation. The cangrelor group had a decreased primary efficacy end point (death, MI, ischemia-driven revascularization, or stent thrombosis at 48 h) of 4.7 vs 5.9% for clopidogrel ($P = 0.005$). The stent thrombosis at 48 h was also decreased in the cangrelor group (0.8 vs 1.4%, $P = 0.01$). There was no significant difference in the primary safety end point of severe bleeding not related to CABG (cangrelor 0.16% vs 0.11% clopidogrel, $P = 0.44$).

Cangrelor was administered for 2 h or the duration of PCI (whichever is longer). The patient must be transitioned to an oral P2Y₁₂ inhibitor. Ticagrelor binds reversibly and non-competitively, explaining why it can be given any time during the cangrelor infusion. Prasugrel and clopidogrel compete for the same receptor, and bind for the life of the platelet, so they will have no effect unless administered after the cangrelor infusion is complete (Table 2). Moreover, ticagrelor's metabolites are equally efficacious with long half-life, and thus still present after the effects of cangrelor have dissipated.

The optimal strategy for using cangrelor remains debated, particularly in STEMI as only a small minority of the patients studied in all CHAMPION studies had STEMI on presentation. Moreover, its utility in the setting of ticagrelor or prasugrel remains unstudied. At present, cangrelor seems particularly beneficial in patients undergoing PCI who cannot tolerate oral DAPT, especially in those treated with intraprocedural bivalirudin [23]. The rapid onset/offset of cangrelor may also be useful in patients with high pretest probability for needing CABG. The BRIDGE Study, which evaluates short-term use in patients undergoing surgery, is ongoing [24].

Ticagrelor versus prasugrel?

Based on the current data, the authors favor the use of ticagrelor or prasugrel over clopidogrel, except where there is clinical concern for high risk for bleeding (in which case a less potent option may be preferable), where the patient profile is considered high-risk for these agents (based on the TRITON or PLATO studies), or where there is a concern for compliance (for twice daily dosing) or cost. However, there are no validated scores or criteria, which guide physicians to choose a particular agent. Based on clinical judgment and available data, we offer one clinical strategy for selecting dual-antiplatelet therapies in STEMI in Fig. 2.

Though these newer agents have been compared with clopidogrel, there have been no head-to-head comparisons between newer agents. Studies have compared their effects on platelet inhibition. The RAPID Study measured the PRUs (platelet reactivity units) in 50 STEMI patients randomized to prasugrel

Table 2. Using IV cangrelor with other P2Y₁₂ inhibitors

Agent	Cangrelor infusion (2 h or duration of the PCI)	After cangrelor infusion
Ticagrelor	180 mg (can give simultaneously)	Can give during or after the infusion
Prasugrel	Hold	60 mg (immediately after)
Clopidogrel	Hold	600 mg (immediately after)

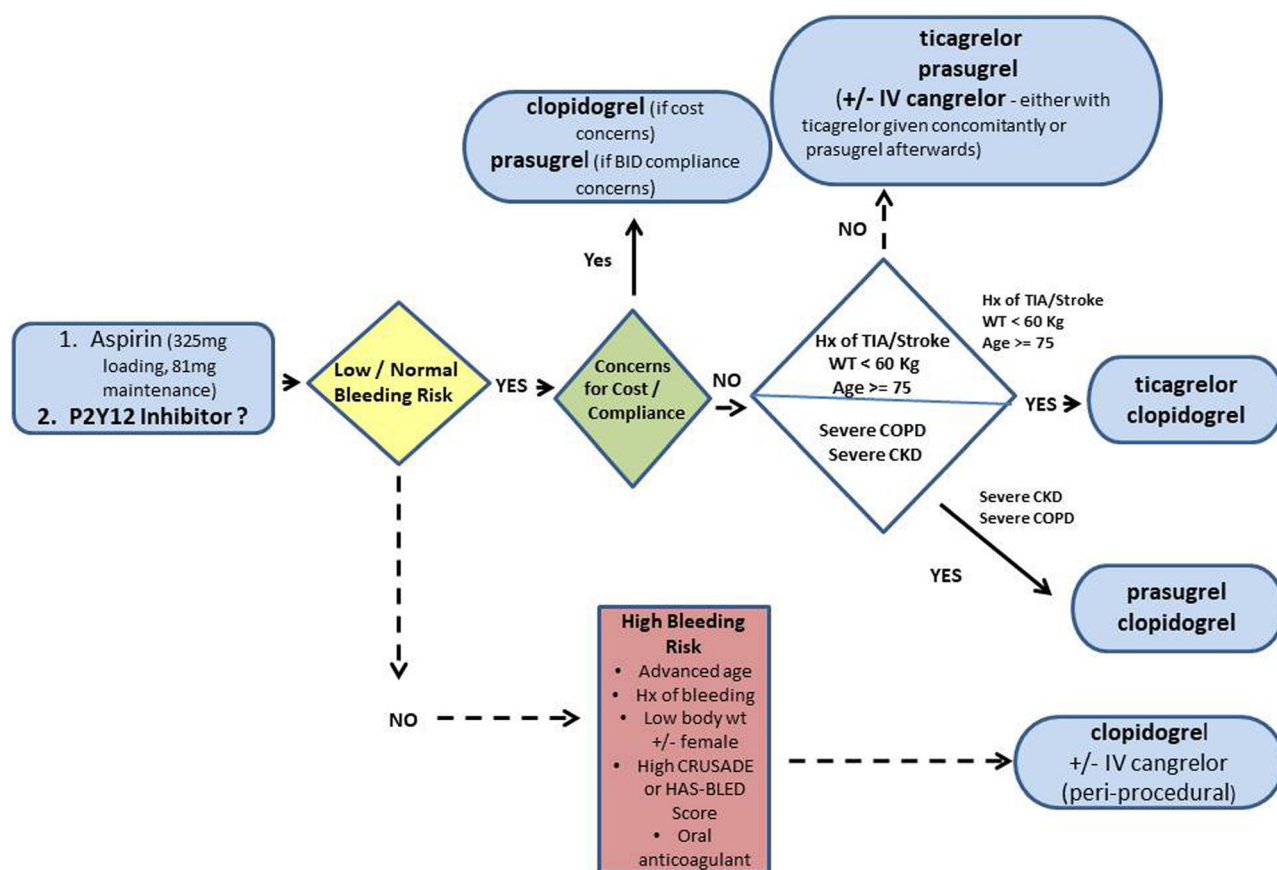


Fig. 2. Strategy for choosing a P2Y12 inhibitor.

(60 mg loading dose) or ticagrelor (180 mg) and found no significant difference (217 and 275 respectively, $P = \text{NS}$) [25].

The SWitching Anti Platelet (SWAP) Study revealed that switching from ticagrelor to prasugrel (in patients with stable CAD) increased PRUs compared with staying on ticagrelor [26]. Interestingly, in the SWAP3 Study, PRUs did decrease when switching from prasugrel to ticagrelor, meeting the criteria of non-inferiority of ticagrelor versus prasugrel [27]. A study to directly compare ticagrelor and prasugrel in ACS with a planned invasive strategy is currently underway in the ISAR-REACT 5 Trial [28].

Peri-procedural antiplatelet decision-making

After selecting a dual-antiplatelet strategy for the STEMI patient, there are still other issues that clinicians might consider, before (e.g., preloading), during (e.g., how to administer), and post PCI (e.g., duration of antiplatelet).

Preprocedural decision-making—to preload or not?

Because of issues of how absorption delays the availability of these P2Y12 inhibitors, which appears more pronounced in STEMI, preloading has been

investigated as a strategy to expedite platelet inhibition. The proposed advantages of such a strategy include reducing the risk of stent thrombosis, periprocedure myocardial infarction, and need for bail-out GP IIb/IIIa. The suggested disadvantages involve increased bleeding risks and delayed revascularization if CABG is needed [29•]. The CREDO Study did not reveal a benefit of clopidogrel pretreatment (combined risk of death, MI, or urgent target vessel revascularization, $P = 0.23$). This was evaluated in a group of patients undergoing elective PCI, and they were only pretreated with 300 mg of clopidogrel [30]. A meta-analysis of seven RCTs (randomized controlled trials, 8608 patients, 25% STEMI patients) revealed that clopidogrel pretreatment did not decrease mortality ($P = 0.17$) but did lower major cardiac events ($P < 0.001$) [31]. A STEMI subgroup analysis revealed an association with clopidogrel pretreatment and a reduction in death ($P = 0.04$) and major coronary events ($P = 0.003$). However, because this analysis pooled dissimilar trials, the results are not seen as definitive. Pretreatment with clopidogrel is currently not the standard of care.

The ATLANTIC Study randomized 1862 patients with STEMI to either prehospital (ambulance) ticagrelor or in-hospital (cath lab) ticagrelor [32]. There was no difference between the prehospital and in-hospital group in the co-primary end points (proportion of patients without $\geq 70\%$ STE segment elevation resolution before PCI, $P = 0.63$, and proportion of patients without TIMI 3 flow in the infarct artery, $P = 0.82$). Notably, there was no difference in the rates of major bleeding between the two groups. It is worth noting that the median time difference between the two groups was only 31 min, which may partially explain why there was no difference in the primary end points. Moreover, in patients not treated with morphine (which slows absorption and may render prehospital administration less efficacious), the primary end point was significantly lower in the pretreatment arm ($P = 0.005$), supporting the argument. In addition, stent thrombosis was lower in the prehospital arm at 24 h and 30 days (0 vs 0.8%, $P = 0.008$, and 0.2 vs 1.2, $P = 0.02$). An exploratory analysis evaluating all of the data during the first 24 h after primary PCI [33] revealed that the prehospital group had a lower composite ischemic end point (10.4 vs 13.7%, $P = 0.039$), stent thrombosis ($P = 0.008$), and MI ($P = 0.031$). That said, for unclear reasons not explained by bleeding, death during the first 24 h was higher in the prehospital group (1.1 vs 0.2%, $P = 0.048$).

At this point, pretreatment with DAPT prior to PCI in patients presenting with DAPT is not routinely recommended. The role of alternative fast-acting intravenous options (cangrelor) may also change the calculus of preloading patients prior to anticipated primary PCI. [34].

Intraprocedural decision-making—to crush or not?

Another strategy in achieving faster and greater platelet inhibition of the oral agents is crushing the pills to increase absorption. A small study demonstrated that crushed clopidogrel given via a nasogastric tube had faster and greater bioavailability [35]. The MOJITO Study was a prospective multi-center trial that randomized patients with STEMI undergoing PCI to crushed ticagrelor (180 mg loading dose) or whole tablets (180 mg) [36]. After 1 h, the P2Y₁₂ reaction units were 168 for the crushed group and 252 for the integral group ($P = 0.006$)—lower associated with increased efficacy—with no difference at 2, 4, and 8 h. The crushed group also had a smaller percentage of patients with high-platelet reactivity (HPR) at 1 h (35 vs 63%, $P = 0.011$). Similarly, the

CRUSH Study evaluated the bioavailability and platelet inhibition of crushed prasugrel (60 mg) versus whole tablets (60 mg) in 52 STEMI patients [37]. Crushed prasugrel had significantly lower PRUs that persisted at 1, 2, and 4 h. HPR rates were also lower with crushed prasugrel for the first 2–4 h (depending on the assay).

For both ticagrelor and prasugrel, it seems reasonable to crush the tablets to achieve more rapid platelet inhibition with little downside.

Post-procedural decision-making: duration of DAPT and the DAPT SCORE

Though not an immediate consideration in STEMI, whether to continue DAPT after 12 months is an important subject that has been evaluated by several recent trials, and this new data has prompted an update to the DAPT guidelines [5••]. The DAPT Study, which is the only one adequately powered to address this question, randomized 9961 patients treated with a drug-eluting stent (DES) after 12 months of DAPT to 18 additional months (30 total months) of thienopyridine (clopidogrel or prasugrel) and aspirin or aspirin and placebo [38•]. It worth noting that patients who had a significant bleed or ischemic event in the first 12 months were excluded from the study. The results revealed a decrease in stent thrombosis (0.4 vs 1.4%, $P < 0.001$), MACE (death, MI, stroke, 4.3 vs 5.9%, $P < 0.001$), and MI (2.1 vs 4.1%, $P < 0.001$) in the prolonged DAPT group. The prolonged DAPT group had an increase in moderate to severe bleeding (2.5 vs 1.6%, $P = 0.001$) and death (2.0 vs 1.5%, $P = 0.05$). The increase in death was attributable to non-cardiovascular causes. This mortality signal was not seen in other prolonged DAPT studies and thought to be cancer-related bleeding that was more prevalent in the DAPT group, or chance.

The benefits of prolonged DAPT specifically in patients with acute MI (STEMI and NSTEMI) were evaluated in a substudy, as 30.7% of patients in the DAPT Study presented with a MI [39]. In the MI group, the benefits of prolonged DAPT in reducing stent thrombosis (0.5 vs 1.9%, $P < 0.001$) and MACCE (3.9 vs 6.8%, $P < 0.001$) were greater than in the group without MI (stent thrombosis 0.4 vs 1.1%, $P < 0.001$, and MACCE 4.4 vs 5.3%, $P = 0.08$). There was bleeding in both groups but less so in the MI group (1.9 vs 0.8%, $P = 0.005$, no MI 2.6 vs 1.7%, $P = 0.007$).

From the DAPT Study, the DAPT Score was developed as a means to risk stratify patients and help determine who may benefit from prolonged DAPT [40•, 41]. This DAPT Score ranges from –2 to 10 and assigns positive points for ischemic risk factors (i.e., one for MI, two for CHF) and negative points for bleeding risk factors (–2 for age ≥ 75). For patients with a DAPT score ≥ 2 , prolonged DAPT was associated with an absolute risk reduction in stent thrombosis and MI that was 8.2× greater than the absolute risk increase in moderate or severe bleeding. On the other hand, patients on prolonged DAPT with a DAPT score < 2 had an increase in bleeding that was 2.4× the absolute reduction in MI or stent thrombosis (Figs. 3 and 4).

Another study that supported the idea of prolonged DAPT in patients with prior MI is the PEGASUS Study [42•]. This study randomized 21,162 with prior MI (1–3 years earlier) and an additional high-risk feature (age ≥ 65 , DM, CKD, multi-vessel CAD, 2nd MI) to ongoing medical management with DAPT using ticagrelor 90 mg twice daily, 60 mg twice daily, or placebo. Over half of these patients (53–54%) had prior STEMI. It is worth noting that most patients (in

Elements of Clinical Prediction Score and Distribution of Score Among Randomized DAPT Study Patients (Derivation Cohort, 11 648 Patients)

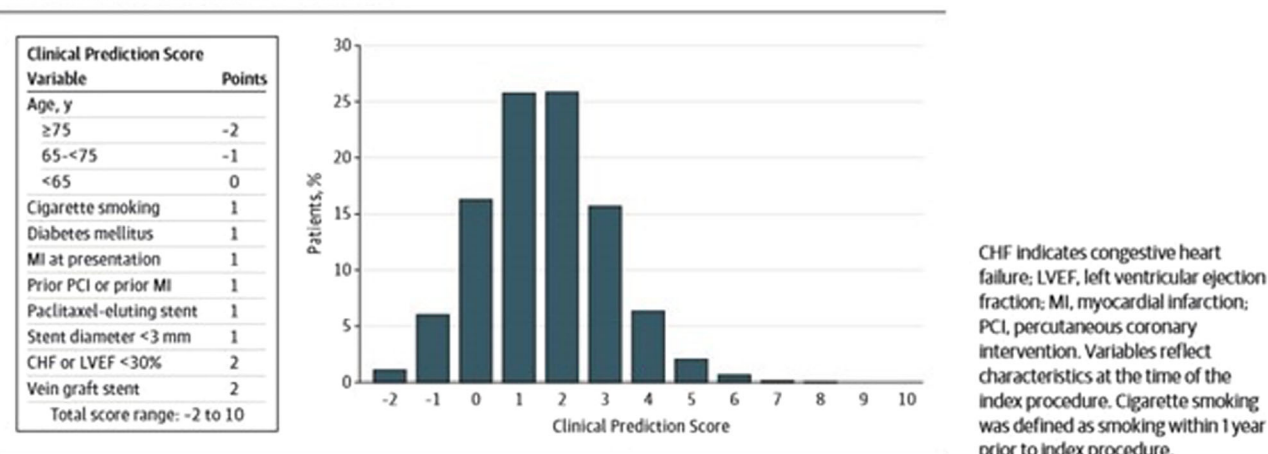


Fig. 3. Elements of the DAPT Score.

contrast to the DAPT Study) had an interruption in DAPT and were enrolled close to 2 years after their MI. Also, they were not excluded for a prior ischemic or bleeding event. The primary efficacy end point (CV death, MI, stroke) was lower in the ticagrelor groups (7.85% for the 90 mg group, 7.77% for 60 mg, 9.04% for placebo, all highly significant). The rates of major bleeding were higher in the ticagrelor groups also (2.6% for 90 mg, 2.3% for 60 mg, 1.06% for placebo, $P < 0.001$ for all). Similar to the DAPT Study, the PEGASUS Study supported prolonged DAPT in select patients with prior MIs.

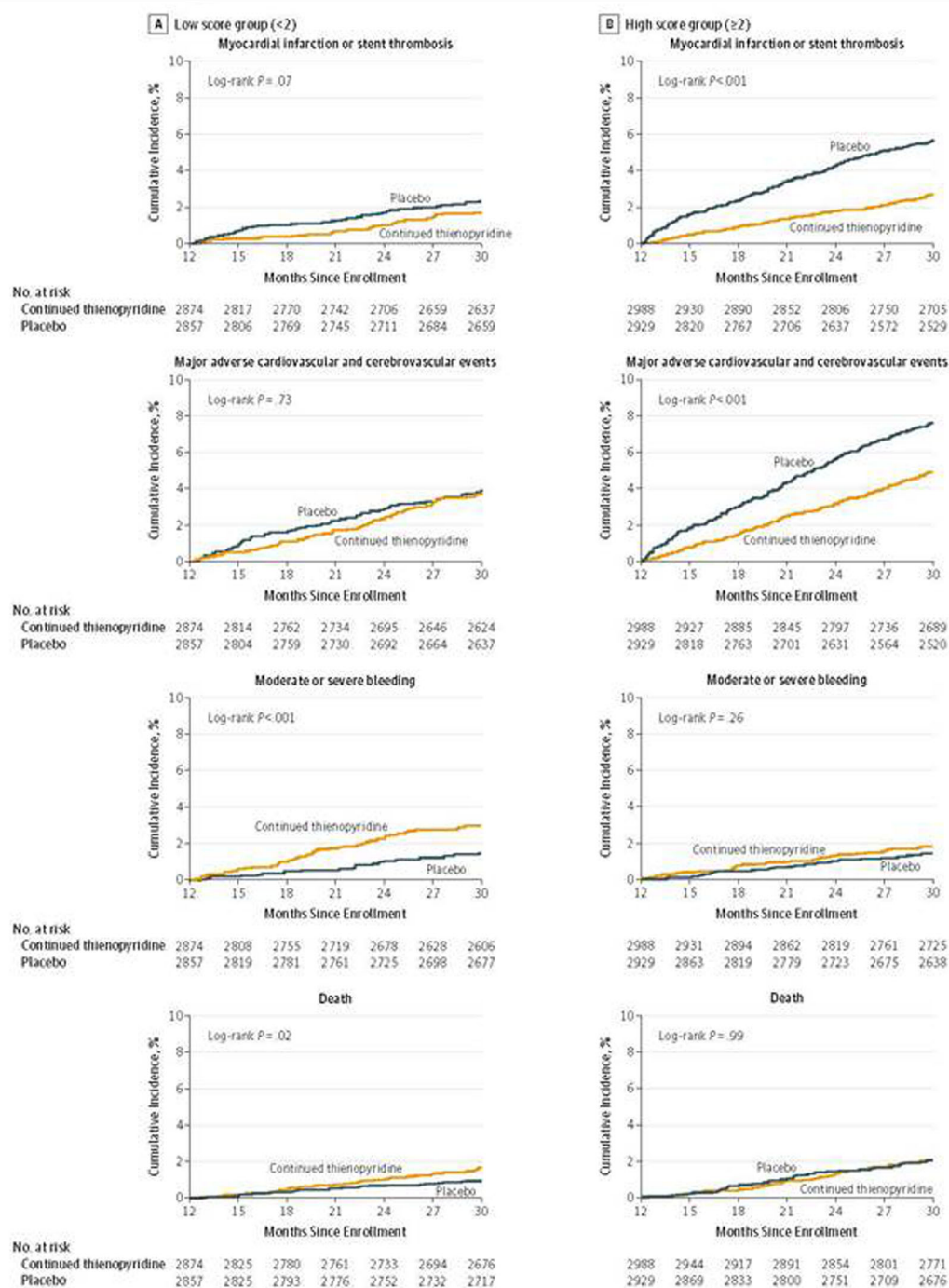
STEMI is associated with late and very late stent thrombosis. In the appropriate patient post STEMI with low baseline bleeding risk, it is reasonable to consider prolonged, if not lifelong, DAPT—using clopidogrel, prasugrel, or ticagrelor—based on these available data in aggregate. Although not specific to STEMI patients, the DAPT score may be a helpful mechanism to select appropriate patients for prolonged DAPT.

Special circumstances—radial STEMI, reloading

Radial STEMI

The use of trans-radial access in PCI for ACS patients has been shown to reduce bleeding complications and in some studies led to a decline in mortality. In the STEMI-RADIAL trial, 707 patients with STEMI were randomized to PCI via a transfemoral or transradial access [43]. The primary end point (bleeding and major vascular complications) was lower in the transradial arm (1.4 vs 7.2%, $P = 0.0001$). The RIFLE-STEACS Study showed the rate of net adverse events significantly favoring the radial approach (13.6 vs 21%, $P = 0.0003$) [44], driven by mortality ($P = 0.02$) and bleeding ($P = 0.026$). The RIVAL STEMI primary PCI subgroup had similar results [45]—primary composite end point (radial 3.1%, femoral 5.2%, $P = 0.026$) and cardiovascular mortality (1.3 vs 3.2%, $P = 0.006$). Interestingly, non-access site bleeding contributed to more than half of all bleeding events, highlighting the significance of spontaneous bleeds and the

Observed Rates of Outcomes From 12 Through 30 Months After Percutaneous Coronary Intervention Among Randomized Patients by Clinical Prediction Score Group in the Derivation Cohort



Moderate or severe bleeding was defined by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries criteria. The number at risk was defined as the number of patients who had not had the event of interest and who were available for subsequent follow-up.

Fig. 4. Outcomes after PCI based on subjects with high- and low-risk DAPT Scores (in the DAPT Study)—figure used with permission from *JAMA* 2016; 315 (16): 1743.

need for careful assessment of the antithrombotic regimen independent of arterial access site.

In the HEAT-PPCI trial [46], STEMI patients undergoing primary PCI were randomized to either bivalirudin or heparin with adjuvant GP IIb/IIIa use in either group. In this study, >80% of patients were treated with a radial approach and >90% received prasugrel or ticagrelor. The 28-day primary composite efficacy outcome (all-cause mortality, stroke, unplanned target vessel revascularization, or recurrent infarction, 5.7% heparin vs 8.7% bivalirudin, $P = 0.01$) and safety outcome of significant bleeding (3.1 vs 3.5%, $P = 0.59$) called for the use of heparin over bivalirudin in STEMI. Although tests for interaction (by radial access or by P2Y12 inhibitor type) were negative, the majority of patients in this trial received prasugrel or ticagrelor and underwent radial access. The favorable efficacy was driven by recurrent MI and TVR. Criticisms of these contrary findings—which were diametrically opposite to those in HORIZONS-AMI [46], EUROMAX [47], and BRIGHT [48]—include observing that HEAT-PPCI was a single-center, open-label, internally validated trial that employed lower heparin dosing (70 U/kg) than guideline-recommended (i.e., 100 U/kg) and employed a high radial access site preference (80% across compared groups). In HEAT-PPCI and EUROMAX trials, >80 and ~50% of patients received prasugrel or ticagrelor, respectively; however, there was no statistically significant interaction between these agents, improved outcomes, or reduced stent thrombosis.

Radial access has been established as safer and with decreased mortality during primary PCI for STEMI, driven primarily by reduced bleeding outcomes. The use of ticagrelor and prasugrel in patients undergoing radial arterial access for STEMI appears safe and reasonable, especially given the reduced bleeding rates associated with radial arterial access. While bivalirudin versus heparin in radial access remains debated, increased stent thrombosis with bivalirudin (as observed in HORIZONS-AMI, HEAT-PPCI, and EUROMAX trials) may support a rationale for more potent antiplatelet coverage (or prolonged bivalirudin dosing) in patients with STEMI undergoing radial arterial access given their safety profile, though the increased efficacy (over clopidogrel) has not been clearly demonstrated with limited available data.

Reloading

Whether patients who are on chronic DAPT require reloading for another PCI, especially in a STEMI, is an important question. The RELOAD Study randomized 166 patients (48% with ACS) on chronic clopidogrel (75 mg daily) to 300, 600, and 900 mg [49]. It found that a 900-mg loading dose leads to greater platelet inhibition compared with the other doses. With respect to prasugrel, there was a prospective study that randomized 64 patients on chronic prasugrel therapy (10 mg daily) to either a 10-, 30-, or 60-mg dose [50]. The 60- and 30-mg doses were associated with a faster and greater reduction in the platelet reactivity index (PRI) than the 10-mg dose at 1 h, and the 60-mg dose was greater than the 30-mg dose at 4 h ($P = 0.05$). Similar results were seen in a study that randomized 60 patients on chronic ticagrelor to a loading dose (180 mg) or maintenance dose (90 mg) [51]. At the 1- and 4-h time points, the loading dose group had a lower PRI ($P = 0.031$) and P2Y12 reaction unit ($P = 0.026$).

With each agent, reloading with a higher dose leads to faster and greater platelet inhibition, although limited safety end points are available. In the selected patient with low-bleeding risk and increased concern for stent thrombosis, reloading with clopidogrel, prasugrel, or ticagrelor may be a reasonable option.

Conclusions

The new P2Y₁₂ inhibitors have been shown to be more potent alternatives to clopidogrel, with further reductions in ischemic end points even in patients suffering from ST elevation myocardial infarction. In the subpopulation of STEMI, the benefits of newer agents such as prasugrel and ticagrelor over clopidogrel for DAPT persist with a reasonable safety profile. Understanding the properties of these agents allows one to individualize therapy to the patient based on his comorbidities and circumstances. Head-to-head comparisons of prasugrel and ticagrelor are underway.

The role of preloading and the implications of IV cangrelor remain debated. Crushing tablets and reloading have been demonstrated as an effective way to expedite platelet inhibition. And while not an immediate consideration, recent studies have demonstrated the benefit of prolonged DAPT therapy in certain STEMI patients, and the DAPT score may be one way to select appropriate patients.

Finally, radial approach to STEMI may allow greater tolerability of more potent agents, though the benefits of these novel agents in the setting of radial access is not entirely clear from the available data.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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