Appropriate Anti-Thrombotic/Anti-Thrombin Therapy for Thrombotic Lesions

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Abstract: Managing coronary thrombus is a challenging task and requires adequate knowledge of the various antithrombotic agents available. In this article, we will briefly analyze the risk-benefit profile of antithrombotic agents, with critical analysis of the scientific evidence available to support their use. Since thrombus consists of platelets and coagulation cofactors, an effective antithrombotic strategy involves using one anticoagulant with two or more antiplatelet agents. Unfractionated heparin traditionally has been the most commonly used anticoagulant but is fast being replaced by relatively newer agents like LMWH, direct thrombin inhibitors, and Factor Xa inhibitors.

In recent years, the antiplatelet landscape has changed significantly with the availability of more potent and rapidly acting agents, like prasugrel and ticagrelor. These agents have demonstrated a sizeable reduction in ischemic outcomes in patients with ACS, who are treated invasively or otherwise, with some concern for an increased bleeding risk. Glycoprotein IIb/IIIa inhibitors have an established role in high risk NSTE ACS patients pretreated with dual antiplatelets, but its role in STEMI patients, treated with invasive approach and dual antiplatelets, has not been supported consistently across the studies. Additionally, in recent years, its place as a directly injected therapy into coronaries has been looked into with mixed results. In conclusion, a well-tailored antithrombotic strategy requires taking into account each patient’s individual risk factors and clinical presentation, with an effort to strike balance between not only preventing ischemic outcomes but also reducing bleeding complications.

Keywords: Antithrombotic therapy, Coronary thrombus, Acute coronary syndrome.

INTRODUCTION

Treatment of thrombotic lesions in the coronary arteries, either in the setting of acute coronary syndrome (ACS) or new lesions formed during elective cases, represents a major challenge. Newly emerging and multiple available pharmacotherapies to address this potentially serious condition can add to this challenge. In this article we will assess the risk benefit profile of various antithrombotic agents, which can help in optimizing the antithrombotic strategy in the catheterization laboratory.

Since the formation and propagation of thrombi involves interactions between activated platelets and the procoagulant factors of the coagulation cascade [1, 2], an optimal antithrombotic strategy consists of inhibiting both pathways enough to stop the development and propagation of thrombus, dissolve it in situ if possible, and balance this act against bleeding complications.

ANTI-COAGULANTS

[Please refer to Table 1 for the dosing of most commonly used anticoagulants]

Heparins (UFH and LMWH)

UFH has been the most commonly used anticoagulant in the catheterization laboratory but its use is limited by vari
A subgroup analysis [15] of patients \((n=4676)\) who underwent PCI in the EXTRACT TIMI 25 trial (LMWH vs. UFH in patients with STEMI treated initially with thrombolytics; \(n=20,506\)) also showed that the primary combined end point of death and myocardial infarction at day 30 occurred less frequently in patients treated with enoxaparin versus UFH (10.7\% vs 13.8\%; \(p<0.001\)), with similar rates of major bleeding (enoxaparin 1.4\% vs UFH 1.6\%; \(p=NS\)).

In a recent randomized trial, ATOLL (STEMI treated with primary angioplasty and intravenous Lovenox or unfractionated heparin; \(n=910\)), the primary end point consisting of death, complication of MI, procedure failure, and major bleeding at 30 days, occurred less frequently with the use of enoxaparin, without achieving statistical significance (28\% vs 34\%; \(RR\ 0.83, CI\ 0.68-1.01; \(p=0.063\)). The main secondary end point evaluating ischemic outcome (death, recurrent MI or ACS, or urgent revascularization) reached significance and demonstrated a 41\% relative risk reduction in favor of enoxaparin (7\% vs 11\%; \(RR\ 0.59, CI\ 0.38-0.91; \(p=0.015\)). Bleeding incidence was equal between the two groups while net clinical benefit (death, complication of MI, or major bleeding) favored enoxaparin (10\% vs 15\%; \(RR\ 0.68, CI\ 0.48-0.97; \(p=0.030\)) [16].

Johanne Silvain et al, performed a meta-analysis of 23 trials including 30,966 patients who underwent PCI (33.1\% primary PCI for STEMI, 28.2\% secondary PCI after fibrinolysis, and 38.7\% with NSTEMI ACS or stable patients). The analysis showed that enoxaparin was associated with a 34\% relative risk reduction (RR 0.66, 95\% CI 0.58 to 0.77; \(P<0.001\)) and a 1.66\% absolute risk reduction of mortality (NNT=60) [Fig. 1, Fig. 2], along with a significant reduction in major bleeding (RR 0.80, 95\% CI 0.67-0.95; \(P=0.009\)) [Fig. 3]. Patients treated with primary PCI for STEMI had even more significant reduction in mortality (RR=0.52, CI 0.42 to 0.64; \(P<0.001\)) with a decrease in the incidence of major bleeding (0.72, 0.56 to 0.93; \(P=0.01\)) [17].

Overall, in light of the evidence stated above, LMWH (enoxaparin) appears to have a favorable risk benefit profile in comparison to UFH in patients who undergo PCI for ACS.

**Direct Thrombin Inhibitors (DTI)**

This class of anticoagulants inhibits thrombin directly as opposed to the indirect acting heparins and has a benefit with regard to no plasma protein binding and, hence, a more predictable response, along with improved inactivation of thrombin, both clot-bound and free [18]. The most commonly used DTI for treatment in ACS is Bivalirudin, a synthetic bivalent analog of hirudin. Two major trials have assessed Bivalirudin role in ACS using an invasive strategy, the ACUITY trial [19] and the HORIZONS-AMI trial [20].

In the ACUITY trial, 13,819 patients with NSTEMI ACS were enrolled, of which 7789 eventually underwent PCI. In the PCI group bivalirudin alone compared to UFH/LMWH with GPIIb-IIIa inhibitor (GPI) had similar ischemic outcomes (9\% vs 8\%, \(p=0.45\)), less major bleeding (4\% vs 7\%, \(p=0.0001\), RR 0.52, 95\% CI 0.40-0.66), and a trend in favor of better net clinical benefit (12\% vs 13\%, \(p=0.057\); 0.87, 0.75-1.00) [21]. Although there is evidence that major bleeding in ACS is associated with higher mortality [22], a one year follow up of the ACUITY PCI subset did not show any difference in mortality or ischemic outcomes despite a reduction in major bleeding [23]. In a post hoc analysis of ACUITY, patients who received clopidogrel more than 30 minutes after PCI or not at all experienced higher ischemic events. In the setting of expected delay or inability to give clopidogrel, a “bivalirudin only” strategy may not be an advisable one [24].

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**Fig. (1).** Pooled event rates and relative risk ratios for major end points in overall cohort of patients undergoing percutaneous coronary intervention (PCI) and in subgroup of patients undergoing primary percutaneous coronary intervention. STEMI=ST elevation myocardial infarction (printed with permission from BMJ, *BMJ* 2012;344:e553 doi: 10.1136/bmj.e553)
In the HORIZON trial, 3,602 patients presenting with STEMI treated with primary PCI were randomized to either a bivalirudin alone or an UFH/GPI arm. The Bivalirudin only arm had reduced 30-day net adverse clinical event rates (9.2% vs 12.1%; p=0.005) driven primarily by reduced bleeding with bivalirudin (4.9% vs 8.3%; p<0.0001). At 1 year [25], and 3 years [26] the net adverse clinical event rates and major bleeding rates were reduced by 17% and 39%, respectively, yet major adverse cardiovascular events were still similar. Notably, bivalirudin use was associated with a significant increase in the rate of acute stent thrombosis (1.3% vs 0.3%; p<0.001), though 30 day rates of stent thrombosis were not significantly different [20]. Additionally, 63.9% and 65.8% of patients in the bivalrudin “alone” arm of ACUITY and HORIZON respectively were pre-treated with open label UFH, which makes drawing definite conclusions difficult.

**Factor Xa Inhibitors**

Factor Xa Inhibitors are a relatively newer class of anticoagulants which are rapidly expanding. Fondaparinux, has been studied in the OASIS-5 [27] and OASIS-6 trials [28] for NSTE ACS and STEMI. Although fondaparinux reduced bleeding events in these studies in comparison to heparins, its use in the patients who underwent PCI was associated with higher rates of catheter thrombosis and coronary complications, leading to hesitation in their use in patients progressing to PCI [28, 29]. Limited data from OASIS 5 and 6 demonstrated that the adjuvant use of UFH, in PCI patients treated with fondaparinux, reduced the incidence of catheter thrombosis to levels comparable to heparins. To understand the role of adjuvant UFH with fondaparinux, in the OASIS-8 trial, low dose UFH (50 U/kg) was compared with standard dose (60-85 U/kg) in 2026 patients, who presented with NSTE ACS and underwent PCI within 72 hours. Bleeding complications were similar with both doses while ischemic outcomes trended in favor of standard dose UFH (4.5% vs 2.9%; P=0.06). Catheter thrombosis rates were also very low (0.5% in the low-dose group and 0.1% in the standard-dose group, P=0.15) [30]. Therefore patients undergoing PCI, who are pre-treated with fondaparinux, should be administered standard dose UFH.
Otamixaban, an intravenous Xa inhibitor has been tested in two phase II trials; one in ACS (SEPIA-ACS) [31], and one in PCI (SEPIA-PCI) [32]. The phase III TAO trial is still underway to further evaluate the efficacy and safety of this agent (clinicaltrials.gov; NCT01076764).

**PLATELET INHIBITORS**

Antiplatelet agents are required to inhibit platelet aggregation in the presence of activators such as ADP, thrombin, and collagen [33, 34], and thereby improving coronary blood flow. Please refer to (Table 1) for the dosing of oral anti-platelets.

**Glycoprotein IIb/IIIa Inhibitors (GPI)**

Since there are multiple pathways for platelet activation, current dual antiplatelet therapy (DAPT) is not enough in some cases to inhibit platelets effectively. GPI, by their inhibitory action on the final common pathway, can provide further platelet inhibition [35]. GPI have demonstrated reduction in the ischemic outcomes in ACS patients treated with an invasive strategy in multiple trials before the use of DAPT, but with a significant increase in bleeding [34-39]. Benefits of GPI were maintained in high-risk troponin positive patients pre-treated with clopidogrel in NSTE ACS patients who underwent PCI in the ISAR REACT 2 study [40]. In STEMI patients, treated with PCI and DAPT, the role of GPI has been conflicting [On-TIME 2 [41], FINESSE [42], BRAVE 3 [43], ADMIRAL [44]]. However, a meta-analysis of 10,085 STEMI patients treated with PCI demonstrated a mortality benefit with GPI in high-risk patients [45].

Coronary patency studies have also been conducted to demonstrate the efficiency of GPI, as patency has been shown to be a surrogate marker for 30 day mortality [46]. In the IMPACT-AMI trial, eptifibatide was given, in conjunction with fibrinolytic therapy to STEMI patients, and angiographic follow up at 90 minutes showed that the highest Eptifibatide dose achieved a 69% higher rate of TIMI grade 3 flow as compared to placebo (66% vs 39%, p=0.006), and
an increased TIMI 2 and 3 flow in other eptifibatide groups [47]. Mixed results on angiographic patency rates and mortality are seen in other trials [48, 49]. An angiographic sub-study of CAPTURE in the post-PTCA angiograms demonstrated higher thrombus resolution rates with abciximab versus placebo (22% vs 43%; p=0.033) [50, 51]. In the PRISM-PLUS study, tirofiban and heparin versus heparin alone in UA/NSTEMI patients, reduced intracoronary thrombus burden (OR=0.77, p=0.022), improved perfusion grade, and decreased severity of the obstruction [52].

**Intracoronary (IC) Versus Intravenous (IV) GPI**

The use of GPI as intracoronary agents has been tested on the basis of achieving higher local concentrations and, hence, better antiplatelet effects. In some small to moderate sized studies IC GPI has shown infarct size reduction, decrease in microvascular obstruction [53], improvement in the left ventricular function [54], and improvement in myocardial blush [55], but no significant difference in the clinical outcomes [56]. Interestingly, there have been meta-analyses in recent years [57, 58] which show a significant mortality benefit with IC GPI, although the studies included in these analyses are relatively small. Recently published, AIDA STEMI (n=2065) [59] is the largest study which tested the role of IC GPI in STEMI patients undergoing primary PCI with hard clinical endpoints. The primary composite endpoint of all-cause mortality, recurrent infarction, or new congestive heart failure at 90 days did not differ with IC or IV use of GPI (7.0% vs 7.6%; OR=0.91; 95% CI 0.64-1.28; p=0.58). Importantly, lower event rates (8%) than expected (12%), coupled with relatively low risk patients (5 % Killip class 3 or 4, and left main or LAD was infarct related artery in 44 %), significantly reduced the power of the study. In summary the role of IC GPI still needs to be established.

The role of IC GPI was further studied in a recently published study (INFUSE AMI) [60], which consisted of 452 patients presenting with STEMI that involved proximal or mid-left anterior descending artery occlusion. Patients were...
randomized in a 2x2 factorial design to a single bolus of IC abciximab at the lesion site versus no abciximab, and manual aspiration thrombectomy versus no thrombectomy. Patients randomized to IC abciximab had a significant reduction in the primary end point of infarct size measured by cardiac MRI (15.2% vs 17.5%; p=0.03), while thrombus aspiration, interestingly, had no significant impact on the outcomes with or without IC abciximab.

Aspirin and Adenosine Diphosphate (ADP) receptor blockers

The role of aspirin in ACS has been studied in multiple studies and two very large meta-analyses [61, 62] showing significant reduction in non-fatal MI and vascular death. Although the long term dose of aspirin is a much debated issue, the ACC/AHA guidelines recommend a loading dose of 162-325 mg of aspirin to all patients with ACS going for PCI.

Thienopyridines are antiplatelet agents directed against P2Y12 receptors on platelets (ADP receptors) and block a key pathway in the activation of the GP IIb/IIIa receptor [63]. Two are pro-drugs, clopidogrel and prasugrel, and require conversion to an active form in the gastrointestinal tract [64], while the other, ticagrelor, is the active agent [Fig. 4].

Clopidogrel, a thienopyridine, demonstrated a reduction in death from cardiovascular causes, myocardial infarction, or stroke in comparison to aspirin alone in 12,562 patients with NSTE ACS (CURE trial) [65]. In a sub study of CURE [66] (patients undergoing PCI, n = 2658), clopidogrel was associated with a 30% relative risk reduction compared to aspirin alone in CV death and myocardial infarction at 30 days (8.8% vs 12.6%, p=0.002) with no significant difference in major bleeding.

To identify an optimal loading dose of clopidogrel, in CURRENT OASIS-7 [67] 25,086 patients with ACS were randomized to either high dose clopidogrel (600 mg loading dose followed by 150 mg daily for one week then 75 mg daily) or standard dose clopidogrel (300 mg load followed by 75 mg daily), out of which 17,232 patients underwent PCI. Although the overall trial was neutral, the primary efficacy outcome (CV death, MI or stroke at 30 days) was reduced significantly in the subgroup who underwent PCI and received high dose clopidogrel, without an increased risk of major bleeding. This result should be interpreted with caution as it was a subgroup analysis. Similarly, high dose clopidogrel (600 mg) was associated with a lower incidence of ischemic events when compared to 300 mg in STEMI patients, who underwent PCI in the HORIZON AMI trial with an equal bleeding incidence [68].

Prasugrel is a thienopyridine with higher potency and a more rapid onset of action than clopidogrel [69, 70]. In TRITON-TIMI 38, 13,608 patients with ACS (10,074 NSTE ACS and 3,534 with STEMI) scheduled for PCI, were randomized to either prasugrel or clopidogrel. Ninety-nine percent of patients underwent PCI and 94% received at least one stent. The primary endpoint of death from CV causes, non-fatal myocardial infarction, or non-fatal stroke was significantly reduced in the prasugrel arm (9.9% vs 12.1%, HR 0.81; 95%, CI 0.73-0.90; P<0.001), along with a reduction in stent thrombosis (2.4% vs 1.1%; P<0.001) [71] (Table 2). The prasugrel arm had a higher incidence of TIMI major bleeding (2.4% vs 1.8%, p=0.03) and demonstrated higher bleeding tendencies in patients with a prior stroke/TIA, age >75 years, or weight <60kg [72, 73].

Ticagrelor, a non thienopyridine oral P2Y12 receptor blocker [Fig. 4], has been shown to have a favorable profile when compared to clopidogrel, secondary to reversible platelet inhibition, minimal hepatic activation, higher potency, and predictable platelet aggregation inhibition levels [74, 75]. In the PLATO trial, 18,624 patients presenting with ACS were randomized to standard treatment with either ticagrelor or clopidogrel [76]. At randomization, an invasive strategy was planned for 13,408 (72%) of the patients out of which 6,575 patients (49%) had presented with STEMI (Table 2). The primary composite endpoint of cardiovascular death, myocardial infarction, and stroke occurred less frequently in the ticagrelor group than in the clopidogrel group (9-0% vs 10.7%, HR 0.84; 95%, CI 0.75-0.94; p=0.0025), as well as all cause mortality (3.9% vs 5.0%; p=0.01) and stent thrombosis (1.3% vs 2.0%; p=0.0054), without an increase in major bleeding [11.6% vs 11.5%, 0.99 [0.89–1.10]; p=0.8803] [77].

Cangrelor, the first intravenous P2Y12 receptor blocker with very rapid onset of action and short half life [78, 79], failed to demonstrate any superiority over existing treatment strategies, in patients with ACS undergoing PCI [80, 81].

DISCUSSION

Intracoronary thrombus encountered in the setting of ACS should be treated with at least two antiplatelet agents and one anticoagulant. If possible, all patients should receive aspirin with one ADP receptor blocking agent. When choosing ADP receptor blockers due consideration should be given to newer agents like prasugrel and ticagrelor, secondary to their more rapid onset of action, better efficacy profile, and improved ischemic outcomes in comparison to clopidogrel. This benefit must be judiciously weighed against a higher incidence of hemorrhagic complications associated with these agents. If for any reason oral antiplatelet agents cannot be administered in a timely fashion, intravenous GPI, with their rapid onset of action, may be considered as a reasonable alternative. Although use of GPI on top of DAPT is certainly recommended in high risk patients presenting with NSTE ACS with or without visible thrombus, evidence for their benefit in the STEMI population, assessed clinically or by surrogate endpoints, is inconsistent at best. Making definite recommendations about their role in STEMI patients, presenting with or without visible thrombus, is even more difficult in the absence of robust data, and their use perhaps should be reserved for high risk patients with large thrombus burden [82]. The impact of adjuvant GPI therapy on patients who underwent thrombectomy for intracoronary thrombus is also not adequately investigated. Thrombectomy in the TAPAS trial (thrombus aspiration compared with conventional treatment during primary PCI for STEMI), in which roughly 90% of patients in both arms received intravenous GPI, was associated with better clinical and angiographic results [83]. Conversely, in the INFUSE AMI study [60] thrombectomy had no bearing upon the outcomes when...
Table 1. Dosings of Anticoagulants and Antiplatelet agents in the treatment of STEMI/NSTEMI/UA

| Patient Received Initial Medical Treatment (With an Anticoagulant and/or Fibrinolytic Therapy) | Patient Did Not Receive Initial Medical Treatment (With an Anticoagulant and/or Fibrinolytic Therapy) |
|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| **ANTICOAGULANTS**                                                                                     |                                                                                                   |
| Bivalirudin [82,84]                                                                                  |                                                                                                   |
| Wait 30 minutes, then give 0.75 mg/kg bolus, then 1.75 mg/kg/hr infusion (Class I rec)                | 0.75 mg/kg bolus, then 1.75 mg/kg/hr infusion                                                     |
| UFH [82,84]                                                                                            |                                                                                                   |
| -IV GPIb/IIa planned: target ACT 200-50 seconds                                                      | -IV GP IIb/IIIa planned: target ACT 200-50 seconds                                                 |
| -No IV GP IIb/IIIA planned: target ACT 250-300 seconds                                               | -No IV GP IIb/IIIA planned: target ACT 250-300                                                    |
| HemoTec, 300-50 seconds Hemochron (Class I)                                                          |                                                                                                   |
| Enoxaparin [85-87]                                                                                   |                                                                                                   |
| -With prior enoxaparin treatment, if last SC dose administered 8-12h earlier or if only 1 SC dose enoxaparin administered, an IV dose of 0.3mg/kg of enoxaparin should be given | 0.5 mg/kg IV bolus                                                                                 |
| -If last SC dose is administered within the prior 8h, then no additional enoxaparin should be given | If procedure is prolonged >2h, or if the operator needs stronger anticoagulation to manage peri-procedural complications, an additional IV bolus of enoxaparin (at ½ of original dose, 0.25 mg/kg) can be used |
| Fondaparinux [84,88]                                                                                 |                                                                                                   |
| Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI |                                                                                                   |
| 2.5 mg IV initially for STEMI patients undergoing PCI                                                |                                                                                                   |
| 2.5 mg SC with 50-60 U/kg IV bolus of UFH recommended                                                |                                                                                                   |
| **THIENOPYRIDINES**                                                                                  |                                                                                                   |
| Clopidogrel [82,84]                                                                                  |                                                                                                   |
| If 600mg given orally, then no additional treatment                                                  | Loading dose 300-600mg orally                                                                      |
| A second loading dose of 300 mg may be given orally to supplement a prior loading dose of 300 mg     | Maintenance dose of 75mg per day (Class I)                                                        |
| (Class I)                                                                                            |                                                                                                   |
| Prasugrel [85]                                                                                       |                                                                                                   |
| No data available to guide decisions                                                                | Loading dose 60mg orally                                                                           |
|                                                                                                     | Maintenance dose 10mg per day (Class I)                                                           |
| Aspirin [85]                                                                                         |                                                                                                   |
| Patients already taking daily aspirin therapy should take 81 mg to 325 mg before PCI (Class I)       | Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI (Class I)   |
|                                                                                                     | It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses (Class IIa) |
| Ticagrelor [85]                                                                                      |                                                                                                   |
| No data available to guide decisions                                                                | Loading dose 180 mg orally                                                                         |
|                                                                                                     | Maintenance dose 90 mg twice daily (Class I)                                                       |

used with or without intracoronary GPI. Two relatively large studies designed to assess the role of thrombectomy in patients with STEMI, TOTAL (ClinicalTrials.gov; Identifier: NCT01149044) and TASTE (ClinicalTrials.gov Identifier: NCT01093404) are underway and may shed some further light on this issue. Similarly, IC administration of GPI, although not supported by robust clinical data [59], has demonstrated improvement in the infarct size and may be used in patients with large visible thrombus.

Regarding choice of anticoagulants, enoxaparin appears to have a better risk benefit profile in comparison to UFH, but lack of an antidote and increased bleeding with renal impairment should be kept in mind. When choosing bivalirudin as an anticoagulant, careful attention should be paid to the fact that, although bivalirudin is associated with reduction in bleeding complications and patients with higher bleeding risk might benefit from this strategy, cases in which GPI are used or expected to be used secondary to patient or lesion
characteristics like heavy thrombus burden, bivalirudin may not provide additional benefit in terms of reduction in bleeding when compared to heparins. Additionally, a higher incidence of stent thrombosis in the initial phase and lack of an antidote should be considered. In patients pre-treated with fondaparinux intravenous UFH must be used during PCI.

CONCLUSION

Managing coronary thrombus entails individualization of therapy to each patient’s unique risk profile and depends on the setting in which coronary thrombus is encountered. An aggressive antithrombotic approach must always be tempered with keen attention to concomitant bleeding complications.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENT

None declared.

ABBREVIATIONS

UFH = Unfractionated Heparin
LMWH = Low Molecular Weight Heparin
ACS = Acute Coronary Syndrome
STEMI = ST Elevation Myocardial Infarction
NSTEMI = Non ST Elevation Myocardial Infarction
NSTE ACS = Non ST Elevation Acute Coronary Syndrome
UA = Unstable Angina
PCI = Percutaneous Coronary Intervention
NNT = Number Needed to Treat
OR = Odds Ratio
HR = Hazard ratio
CI = Confidence Interval

REFERENCES

[1] Andrews RK, Berndt MC. Platelet physiology and thrombosis. Thrombosis Research 2004; 114: 447-453.

[2] Jackson SP, Nesbitt WS, Kulkarni S. Signaling events underlying thrombus formation. J Thromb and Haemost 2003; 1: 1602-1612.

[3] Schulz S, Mehilli J, Neumann FJ, Schuster T, Massberg S, Valina C, et al. ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. Eur Heart J 2010; 31: 2482-91.

[4] Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, et al. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURE/OASIS-8 randomized trial. JAMA 2010; 304: 1339-49.

[5] Brener SJ, Moliterno DJ, Lincoff AM, Steinbuhl SR, Wolski KE, Topol EJ. Relationship, between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. Circulation 2004; 110: 994-8.

[6] Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin in patients with high-risk non-ST-segment elevation myocardial infarction. N Eng J Med 2006; 354: 1477-88.

[7] Cheng S, Moreau DA, Sloan S, Antman EM, Sabatine MS. Predictors of Initial Nontherapeutic Anticoagulation With Unfractionated Heparin in ST-Segment Elevation Myocardial Infarction. Circulation 2001; 119: 1195-1202.

[8] Fareed J, Jeske W, Hoppensteadt D, Clarizio R, Walenga JM. Low-molecular-weight heparins: pharmacologic profile and product differentiation. Am J Cardiol 1998; 82(5B): 3L-10L.

[9] Cohen M, Demers, C, Gurfinkel EP, Turpie AGG, Fromell GJ, et al. A comparison of Low-Molecular weight heparin with unfractionated heparin for unstable coronary artery disease. N Eng J Med 1997; 337(7): 447-52.

[10] Antman EM, McCabe CH, Gurfinkel EP, Fromell GJ, et al. Enoxaparin Prevents Death and Cardiac Ischemic Events in Unstable Angina/NQ-Wave Myocardial Infarction: Results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. Circulation 1999; 100: 1593-1601.

[11] Fergusson JJ, Califf RM, Antman EM, Cohen M, et al. Enoxaparin vs Unfractionated Heparin in High-Risk Patients with Non-ST-Segment Elevation Acute Coronary Syndromes Managed With an Intended Early Invasive Strategy. JAMA 2004; 292(1): 45-54.

[12] Blazing MA, de Lemos JA, White HD, Fox KAA, et al. Safety and Efficacy of Enoxaparin vs Unfractionated Heparin in patients with non-ST-Segment Elevation Acute Coronary Syndromes: Who Receive Ticofiban and Aspirin. JAMA 2004; 292(1): 55-64.

[13] Cohen M, Mahaffey KW, Pieper K, Pollack CV, et al. A Subgroup Analysis of the Impact of Prerandomization Antithrombin Therapy on Outcomes in the SYNERGY Trial. J Am Coll Cardiol 2006; 48(7): 1346-54.

[14] Gibson CM, Murphy SA, Montalescot G, et al. Percutaneous coronary intervention in patients receiving enoxaparin or unfractionated heparin after fibrinolytic therapy for ST-segment elevation myocardial infarction in the ExTRACT-TIMI 25 trial. J Am Coll Cardiol 2007; 49: 2238-46.

Table 2. Trials Comparing Newer Antiplatelet Agents to Clopidogrel

| Trial | Condition | Efficacy endpoint | Safety endpoint |
|-------|-----------|------------------|----------------|
| TRITON TIMI 38 (Prosugrel vs. Clopidogrel) | ACS patients scheduled for PCI (n=13608) | Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke | 9.9 vs. 12.1% P<0.001 Major bleeding 2.4 vs. 1.8% P=0.03 |
| PLATO-Invasive (Ticagrelor vs. clopidogrel) | ACS patients scheduled for PCI (n=13408) | Death from vascular causes, myocardial infarction, or stroke | 9.0 vs. 10.7% P=0.0025 Major bleeding 3.2 vs 2.9% P=0.37 |
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[17] Silvain J, Béguy F, Barthélémy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 2012; 344: e553.

[18] Weitz JI, Crowther M. Direct thrombin inhibitors. Thrombosis Research 2002; 106: 275-284.

[19] Stone GW, McLaurin BT, Cox DA, Bertrand ME, et al. Bivalirudin for Patients with Acute Coronary Syndromes. N Engl J Med 2006; 355(21): 2203-2216.

[20] Stone GW, Wiznitzer B, Guagliumi G, Peruga JZ, et al. Bivalirudin during Primary PCI in Acute Myocardial Infarction. N Engl J Med 2008; 358(21): 2218-2230.

[21] Gregg W Stone, Harvey D White, E Magnus Ohman, Michel E Bertrand, A Michael Lincoff et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet 2007; 369: 907–19.

[22] Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006; 114; 774-782.

[23] White HD, Ohman EM, Lincoff AM, et al. Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Cardiol 2008; 52: 807-814.

[24] Lincoff AM, Steinhubl SR, Manoukian SV, et al. Influence of Timing of Clopidogrel Treatment on the Efficacy and Safety of Bivalirudin in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes. J Am Coll Cardiol 2008; 53: 1270-1276.

[25] Mehran R, Lansky AJ, Wiznitzer B, Guagliumi G, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomized controlled trial. Lancet 2009; 374: 1149-59.

[26] Stone GW, Wiznitzer B, Guagliumi G, et al. on behalf of the HORIZONS AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS AMI): final 3-year results of a multicentre, randomised controlled trial. Lancet 2008; 372: 537-546.

[27] Ellis SG, Tendera M, de Belder MA, van Boven AJ, et al. Facilitated PCI in patients with STElevation myocardial infarction. N Engl J Med 2008 May 22; 358(21): 2205-17.

[28] Stone GW, Wiznitzer B, Guagliumi G, Peruga JZ, Brodie BR, et al. HORIZONS-AMI Trial Investigators. Bivalirudin during percutaneous coronary intervention in acute myocardial infarction. N Engl J Med 2008; 358: 2218–2230.

[29] Montalescot G, Barragan P, Wittenberg O, Ecolan P, et al. for the ADIMARIAL Investigators. Platelet Glycoprotein IIb/IIIa Inhibition with Coronary Stenting for Acute Myocardial Infarction. N Engl J Med 2001; 344: 1895-1903.

[30] De Luca G, Navarese E, Marino R. Risk profile and benefits of Gp IIb-IIIa inhibitors among patients with STElevation myocardial infarction treated with primary angioplasty: A meta-regression analysis of randomized trials. Eur Heart J 2009; 30: 2705–2713.http: //www.nejm.org/toc/nejm/344/25/.

[31] Simes RJ, Topol EJ, Holmes DR Jr, White HD, et al. Link between the angiographic subacute and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. Circulation 1995; 91(7): 1923-8.

[32] Ohman, EM, Kleiman NS, Gacioch G, Worley SJ, et al. Combined Accelerated Tissue-Plasminogen Activator and Platelet Glycoprotein IIb/IIIa Inhibitor Receptor Blockade with Integritin in Acute Myocardial Infarction: Results of a randomized, placebo-controlled, dose-ranging trial. Circulation 1997; 95: 846-54.

[33] Zeizmer U, Zahn R, Schiele R, et al. Early epifibatide improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized-integritin in acute myocardial infarction (INTAMI) pilot trial. Eur Heart J 2005; 26: 1971-1977.

[34] Gibson M, Kirtane AJ, Murphy SA, et al. Early initiation of epifibatide in the emergency department before primary percutaneous coronary intervention for ST-elevation myocardial infarction: results of the Time to Integriplin Therapy in Acute Myocardial Infarction (TITU-M) TIMI 34 trial. Am Heart J 2006; 152: 668–675.

[35] van den Brand M, van Eng, PG, de Scherder I, et al. Assessment of coronary angiograms prior to and after treatment with abciximab, and the outcome of angioplasty in refractory unstable angina patients: Angiographic results from the CAPTURE trial. Eur Heart J 1999; 20(21): 1572-8.

[36] The Capture Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997; 349: 1429-35.
[52] Zhao Qx, Theroux P, Snappin SM, Sax FL. Intracoronary thrombus and platelet glycoprotein Iib/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction. Angiographic results from the PRISM-PLUS trial. PRISM-PLUS Investigators. Circulation 1999; 100(15): 1609-15.

[53] Thiele H, Schneider K, Friedenberger J, Eitel I, et al. Intracoronary Compared with Intravenous Bolus Abciximab application in patients with ST-Elevation myocardial infarction undergoing primary percutaneous coronary intervention: The randomized Leipzig immediate percutaneous coronary intervention Abciximab IV versus IC in ST-Elevation Myocardial Infarction Trial. Circulation 2008; 118: 49-57.

[54] Eitel I, Friedenberger J, Fuernau G, Dumjahn A, et al. Intracoronary versus intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: 6-month effects on infarct size and left ventricular function. Clin Res Cardiol 2011; 100: 425-432.

[55] Gu YL, Kampina MA, Wieringa WG, Fokkema ML, et al. Intracoronary versus Intravenous Administration of Abciximab in patients with ST-Segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: The comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial. Circulation 2010; 120: 2709-2717.

[56] Bertrand OF, Rodes-Cabau J, Larose E, et al. Intracoronary compared to intravenous abciximab and high-dose bolus compared to standard dose in patients with ST-segment elevation myocardial infarction undergoing transradial primary percutaneous coronary intervention: a two-by-two factorial placebo-controlled randomized study. Am J Cardiol 2010; 105: 1520-27.

[57] Shimada YI, Nakra NC, Fox JT, Kanei Y. Meta-analysis of prospective randomized controlled trials comparing intracoronary versus intravenous abciximab in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Am J Cardiol 2011; 109: 624-8.

[58] Friedland S, Eisenberg MJ, Shimon Y. Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein Iib/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol 2011; 108: 1244-51.

[59] Thiele H, Wöhrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. Lancet Feb 2012.

[60] Stone GW, Machara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction. JAMA 2012; DOI: 10.1001/jama.2012.421.

[61] Antiplatelet trialists’ Collaboration. Collaborative overview of randomized trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308: 81-106

[62] Antiplatelet Trialists’ Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.

[63] Dorsam RT, Kunapuli SP. Central role of the P2Y12 receptor in various categories of patients. BMJ 2002; 324: 71-86.

[64] Michelson AD. P2Y12 antagonism: promises and challenges. Arterioscler Thromb Vasc Biol 2008; 28: s33-s38.

[65] Yusuf S, Zhao F, Mehta SR, Chrolavicius S, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001 Aug; 345(7): 494-502.

[66] Mehta SR, Yusuf S, Peters RJG, Bertrand ME, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001; 358: 527-33.

[67] Mehta SR, Bassand JP, Chrolavicius S, Diaz R, et al. Dose comparisions of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010 Sep; 363(10): 930-42.

[68] Dangas G, Mehran R, Guglielmi G, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. J Am Coll Cardiol. 2009 Oct 6; 54(15): 1438-46.

[69] Wallentin L, Varenhorst C, James S, Erlinge D, et al. Prasugrel achieves greater and faster P2Y12 receptor-mediated platelet inhibitory effects than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J 2008; 29: 21-30.

[70] Wallentin L. P2Y12 inhibitors: differences in properties and mechanism of action and potential consequences for clinical use. Eur Heart J 2009; 30: 1964-1977.

[71] Wiviott SD, Braunwald E, McCabe CH, Horvath I, et al. Intensive oral antplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomized trial. Lancet 2008; 19: 1353-63.

[72] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, et al. Prasugrel versus Clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15.

[73] Murphy SA, Antman EM, Wiviott SD, Weerakkody G, et al. Reduction in recurrent cardiovascular events with prasugrel compared with clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. Eur Heart J 2008; 29: 2473-2479.

[74] Husted S, Emanuelsson H, Heptinstall S, Sandset PM, et al. Pharmacodynamic, pharmacokinetics, and safety of oral reversible P2Y12 inhibitor AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006; 27: 1038-1047.

[75] Husted S, van Giezen JJ. Ticagrelor: the First Reversibly Binding Oral P2Y12 Receptor Antagonist. Cardiovasc Ther 2009; 27: 259-74.

[76] Wallentin L, Becker RC, Budaj A, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with Acute Coronary Syndromes. N Engl J Med 2009; 361: 1045-1047.

[77] Christopher P Cannon, Robert A Harrington, Stefan James, Diego Ardissino, Richard C Becker, Håkan Emanuelsson. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010 Jan 23; 375(9711): 283-93.

[78] Storey RF, Oldroyd KG, Wilcox RG. Open multicentre study of the P2T receptor antagonist AR-C69931MX assessing safety, tolerability and activity in patients with acute coronary syndromes. Thromb Haemost 2005; 85: 401-407.

[79] Greenbaum AB, Grines CL, Bittl JA, et al. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: Results from a 2-part, phase II, multicenter, randomized, placebo and active-controlled trial. Am Heart J 2006; 151: 689.e1-10.

[80] Stone GW, Dangas G, Lincoff M, Gibson CM, Stone GW, et al. Intravenous Platelet Blockade with Cangrelor during PCI. N Engl J Med 2009; 361: 2330-2341.

[81] Harrington RA, Stone GW, McNulty S, White HD, et al. Platelet Inhibition with Cangrelor in Patients Undergoing PCI. N Engl J Med 2009; 361: 2318-29.

[82] Frederick G, Kusterer, Mary Hand, Sidney C. Smith et al. Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. J Am Coll Cardiol 2009; 54: 2205-2241.

[83] Svilaa T, Vlaar PJ, van der Horst IC, et al. Thrombus Aspiration during Primary Percutaneous Coronary Intervention. N Engl J Med 2008; 358: 557-567.

[84] Wright RS, Anderson JL, Adams CD, et al. 2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction. J Am Coll Cardiol 2011; 57: 1920-1959.

[85] Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011; 124(23): e574-651.

[86] Sanchez-Pena P, Hulot JS, Urien S, et al. Anti-factor Xa kinetics after intravenous enoxaparin in patients undergoing percutaneous coronary intervention: a population model analysis. Br J Clin Pharmacol 2005; 60: 364-73.
Montalescot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med 2006; 355: 1006-17.

Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2008; 51: 210-47.