Current Atherosclerosis Reports (2019) 21: 22
https://doi.org/10.1007/s11883-019-0782-x

EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Optimal Antithrombotic Therapy for Patients with STEMI Undergoing PCI at High Risk of Bleeding

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Published online: 17 April 2019

Abstract

Purpose of Review In the review, we briefly describe antithrombotic drugs and the use evidence from evidence-based medicine to elucidate the optimal antithrombotic management for patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary stenting (PCI) at high risk of bleeding.

Recent Findings Mandatory use of intravenous anticoagulants and dual antiplatelet agents is the cornerstone strategy in acute and long-term antithrombotic management to optimize the clinical benefit of patients with STEMI undergoing PCI. Nevertheless, with the increasing occurrence of STEMI in old population with high risk of bleeding and renal insufficiency, as well as the specificity of high bleeding risk groups, the optimization of antithrombotic therapy still remains uncertain.

Summary Bivalirudin is the optimized intravenous anticoagulant agent for these patients based on the guideline recommendations and clinic data. Timely and potent ticagrelor and prasugrel with aspirin usage can increase the clinical benefit for the patients without increasing the clinical bleeding risk. At present, the multi-center, prospective clinical studies of EVOLVE short DAPT, MASTER DAPT, and POEM trials, targeting patients with high risk of bleeding, are in experimental stage. These clinical trials will provide more objective and optimal antithrombotic management strategy for the patients.

Keywords Antithrombotic therapy · Acute ST-segment elevation myocardial infarction (STEMI) · Percutaneous coronary intervention (PCI) · High risk of bleeding · Bivalirudin

Introduction

Global evidence-based guidelines have confirmed that acute ST-segment elevation myocardial infarction (STEMI), a major cause of morbidity, mortality, and disability, is an important public health problem worldwide [1, 2•, 3]. In recent years, STEMI comprises 25–40% of myocardial infarction (MI) presentations and the overall incidence of STEMI is decreasing. With the development of reperfusion therapy, percutaneous coronary stenting (PCI), antithrombotic therapy, and secondary prevention strategies, STEMI mortality and disability rates have decreased and patients with cardiovascular disease benefited significantly. However, both in-hospital and 1-year mortality from STEMI persisted at relatively high levels. Data from the ACCF/AHA guideline for STEMI published in 2013 indicated that in-hospital and 1-year mortality of STEMI patients were 5–6% and 7–18%, respectively [1]. Furthermore, the ESC guidelines for STEMI published in 2017 showed that in-hospital and 1-year mortality of STEMI patients were 4–12% and ~ 10%, respectively [2•].

The preferred treatment for STEMI is timely PCI vascular reperfusion to achieve early infarct revascularization. The key factors for STEMI are the calcification, rupture, or erosion of atherosclerotic plaque following by coronary artery thrombosis and occlusion [4–6]. The main pathological basis involved is the

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This article is part of the Topical Collection on *Evidence-Based Medicine, Clinical Trials and Their Interpretations*

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cellular platelet effect and plasma coagulation process. Therefore, antithrombotic therapy, including antiplatelet therapy and anticoagulant therapy, is the cornerstone strategy to optimize clinical outcomes in patients with STEMI undergoing PCI. However, with increased incidence of STEMI in patients at high risk of bleeding in old age people with severe complications, as well as the specificity of high-bleeding risk groups, antithrombotic drugs are often forbidden or only used with caution in clinical setting [7, 8]. This undoubtedly poses a tough challenge to routine and effective antithrombotic therapy. Therefore, how to choose antiplatelet and anticoagulant agents to optimize the clinical outcomes in patients at high risk of bleeding is still a challenge. The review aims to briefly describe antithrombotic drugs and the use evidence from evidence-based medicine to elucidate the optimal antithrombotic management.

Methodology

We conducted a narrative review of the literature using the PubMed database to search for randomized controlled clinical trial or meta-analysis or review published in English. Our search keywords included "antithrombotic therapy," "acute ST-segment elevation myocardial infarction," "percutaneous coronary intervention," "high risk of bleeding," "high bleeding risk," "bivalirudin," antiplatelet therapy," "optimal antithrombotic therapy." For all manuscript captured by our search, we also reviewed all of the references in each in order to search for other relevant studies to include in our references.

Theoretical Basis for Antithrombotic Therapy in STEMI

Injury to the arterial vessel wall exposes the subendothelial layer and leads to recruitment and activation of platelets, as well as excessive generation of thrombin. Following adhesion, platelets release many activating factors, mainly thromboxane A 2, ADP, and thrombin, which activate platelet signaling pathways leading to adhesion and further recruitment of platelets, and activation of circulating platelets. The final step of the signal pathways is the conversion of the platelet glycoprotein IIb/IIIa receptor into its active form, which binds to soluble adhesive substrates, including fibrinogen and von Willebrand factor, and leads to platelet aggregation and formation of an occlusive thrombus mediated by platelet-fibrin interaction [9, 10]. Vascular injury also exposes subendothelial tissue factor, which activates the coagulation cascade, leading to thrombin generation. Thrombin can convert fibrinogen to activated type fibrin, an essential component of arterial thrombus. Thrombin is also one of the most potent platelet activators by binding to protease-activated receptors (PARs) on the platelet membrane. Notably, even though a modest amount of thrombin is produced as a result of the coagulation cascade, the surface of activated platelets is the main source of circulating thrombin [11, 12].

Currently, the target of cellular mediators, receptors, and action sites for platelets and coagulation pathways, many antiplatelet and anticoagulants drugs are gradually applied to the antithrombotic management of STEMI patients.

Definition of Patient with STEMI at High Risk of Bleeding

Patients with STEMI at high risk of bleeding are severely challenged in implementing antithrombotic management strategies, which require medical workers to evaluate the risk of embolism and bleeding more accurately. Currently, although there is no standard for the clinical definition of patient with high bleeding risk, based on the CRUSADE score, PRECISE DAPT score, and DAPT Risk score as well as the LEADERS FREE trial, patients with STEMI at high risk of bleeding are defined to meet at least one of the following criteria (Table 1) [13, 14••]. Age and renal insufficiency are the main references in evidence-based clinical trials.

Optimized Management Strategy of Antithrombotic Drug

Intravenous Anticoagulant Therapy

The acute phase of STEMI is characterized by a complex pathophysiological process with blood hypercoagulability and high-risk thrombosis, which, along with the delay due to hospital admission process or first medical contract with coronary angiography, underscores the need for fast-acting, intravenous antithrombotic therapies providing effective blockade of thrombin-mediated effects and platelet signaling pathways. Currently, the commonly used intravenous anticoagulants are thrombin and factor Xa inhibitors, which include unfractionated heparin (UFH), low-molecular-weight heparin (LMWHs), bivalirudin, and fondaparinux. Because of the high rate of catheter thrombosis recorded in the OASIS

Table 1 Inclusion criteria of patients with high bleeding risk

Age ≥ 75 years old
Renal insufficiency (eGFR < 60 ml/min or cCr < 60 ml/min)
Baseline Hb < 11 g/dl (or anemia requiring TF during the prior 4 weeks)
Thrombocytopenia (< 100,000/mm^3)
Hospital admission for bleeding during the prior 12 months
Planned major surgery (within 1 year)
Non-skin cancer diagnosed or treated ≤ 3 years
Planned daily NSAID (other than aspirin) or steroids for ≥ 30 days after PCI
Expected non-compliance to prolonged DAPT for other medical (nonfinancial) reasons

NSAID, non-steroidal anti-inflammatory drug; *TF*, blood transfusion

clinical trial published in 2006, fondaparinux has been less favorable in the latest guidelines.

LMWHs are derived from UFH by chemical or enzymatic depolymerization and are about one-third of the molecular weight of UFH. LMWHs have longer plasma half-life, and lower incidence of HIT when compared with UFH. The major limitation of LMWHs is that their usage is generally restricted in patients with renal dysfunction (Cr < 30 mL/min), due to increased risk of bleeding [15, 16]. In recent years, the use of intravenous anticoagulant has been defined in multi-guidelines for patients with STEMI undergoing PCI. For patients with STEMI undergoing PCI, both the 2013 ACC/AHA and 2018 ESC guidelines on myocardial revascularization [17] give class I recommendation for UFH (level of evidence C). Bivalirudin is listed as class I recommendation in the 2013 ACC/AHA guidelines (level of evidence B) and class IIb recommendation in 2018 ESC guidelines (level of evidence A). However, there is still no guideline regarding optimized anticoagulant strategy for PCI process in patients at high risk of bleeding. Franchi F et al. [18] believe that bivalirudin is a more optimal anticoagulant than heparin. However, the optimal clinical benefit of anticoagulant management for patients at high risk of bleeding has always been controversial.

In 2016, a meta-analysis [19] on patients ($n = 17,294$) with STEMI undergoing PPCI demonstrated that bivalirudin reduced the risk of major bleeding (OR 0.65, $P = 0.006$), decreased all-cause mortality (OR 0.81, $P = 0.03$), and cardiac death (OR 0.69, $P = 0.001$), when compared with heparin. Meanwhile, intravenous infusion of bivalirudin for 3 h (1.75 mg/kg/h) still reduced the risk of bleeding (OR 0.28, $P = 0.001$) and did not increase the risk of acute stent thrombosis (OR 0.81, $P = 0.71$). The MATRIX-STEMI trial published in 2016 [20••] indicated that there were no significant differences in the risk of major adverse cardiovascular events (MACEs) and net adverse clinical events (NACEs) by using bivalirudin alone compared with heparin, although patients treated with bivalirudin had a modestly higher incidence of definite 30-day stent thrombosis, the rate of acute (≤ 24 h) stent thrombosis was similar between treatment groups. However, a subgroup analysis of patients at high risk of bleeding (eGFR< 60 ml/min) suggested that bivalirudin reduced the risk of composite primary endpoint event (major adverse cardiovascular events and net adverse clinical events) (OR 0.50, $P = 0.004$). In the ACUITY [21] trial published in 2009 involving 2441 patients with STEMI, bivalirudin alone can reduce the risk of non-CABG-related major bleeding compared with unfractionated heparin combined with glycoprotein IIb/IIIa inhibitors in individuals at high risk of bleeding (age ≥ 75 years) (6.1% vs 12.3%). Recent trials of SWEDEHEART [22] and HEAT PPCI [23] have shown that there was no significant difference between bivalirudin and heparin based on subgroup analysis of major adverse cardiovascular events and/or composite endpoint of major bleeding events. In summary, although all evidence-based data are from subgroup analysis of large-scale clinical trials, or the study population is not limited to patients with STEMI, the evidence suggests that bivalirudin should be considered in patients with STEMI who are at high risk of bleeding and undergoing PPCI, and thus a more optimal anticoagulation regimen in these patients' cohorts.

Intravenous Antiplatelet Therapy

The main mechanism of glycoprotein IIb/IIIa inhibitors (GPIs) is to target the final pathway of platelet aggregation, competing with von Willebrand factor and fibrinogen for glycoprotein IIb/IIIa receptor binding and provide fast and potent antiplatelet effects [24]. Currently, the widely used GPIs intravenous antiplatelet agents include abciximab, eptifibatid, tirofiban, and the P2Y 12 receptor inhibitor cangrelor. In 2005, a clinical trial including 11 studies on patients with STEMI ($n = 27,115$) showed that abciximab-assisted antithrombotic management can reduce 30-day and long-term mortality in patients treated with direct angioplasty [25]. However, abciximab increased major bleeding risk in patients treated with thrombolysis. According to a large number of evidence-based data, a series of small-scale trials have indeed confirmed the safety and effectiveness of facilitated PCI therapeutic strategies by using GPIs alone or in combination with low-dose thrombolytic drug [26]. However, not all experimental studies confirm the effectiveness of GPIs.

In the FINESSE [27] trial conducted by ELLIS et al. published in 2008, facilitated PCI strategies with the abciximab monotherapy, or in combination with low-dose thrombolytic drug in patients with STEMI was evaluated. The experimental data indicated that the drop rate of ECG ST-T segment within 60–90 min was higher in combination-facilitated PCI (43.9%) and abciximab-facilitated PCI (33.1%), in comparison with primary PCI (31.0%) ($P = 0.01$, $P = 0.003$). There was no significant difference among the three groups in the primary endpoint events (all-cause death, ventricular fibrillation within 48 h, cardiogenic shock, and 90-day composite event of congestive heart failure) or mortality within 90 days. The primary endpoint events occurred in 9.8%, 10.5%, and 10.7% of the patients in the combination-facilitated PCI group, abciximab-facilitated PCI group, and primary-PCI group, respectively ($P = 0.55$); 90-day mortality were 5.2%, 5.5%, and 4.5%, respectively ($P = 0.49$). Compared with abciximab in primary PCI, facilitated PCI group improved the clinical benefit of the patient either using abciximab monotherapy or in combination. Although results from evidence-based medicine have confirmed the effectiveness of abciximab in the application of PPCI, the risk of major bleeding event is still a limitation of current applications. In the HORIZON-AMI trial [28], compared with heparin in combination with GPIs, bivalirudin reduced the risk of bleeding within 30 days, thereby reducing

net clinical adverse events. More importantly, bivalirudin can, to some extent, reduce the bleeding complications, which in turn can significantly reduce the patients' mortality after 1 and 3 years [29, 30]. Evidence from evidence-based medicine has also confirmed that clinical benefit of GPIs can be obtained in patients with STEMI undergoing PCI. However, the clinical benefit of GPIs is mainly in the era of balloon angioplasty, namely before extensive use of dual antiplatelet therapy, novel stent technology, radioactive arterial intervention, and anticoagulant. In addition, the clinical benefit of GPIs therapy is at the cost of an increased bleeding risk and thrombopenia. Therefore, as the safety and effectiveness of alternative treatments are evolving, the role of GPIs has been reduced and it is regarded as selective rather than routine use, not to mention in clinical application of patients at high bleeding risk.

Oral Antiplatelet Therapy

In addition to intravenous antithrombotic drugs, oral antithrombotic drugs after stent implantation should be emphasized, which will undoubtedly produce a significant clinical benefit for long-term prognosis. Oral antithrombotic therapy is the cornerstone of the acute and long-term treatment of patients with STEMI. Currently, the widely used agents available for clinical use include aspirin, clopidogrel, prasugrel, and ticagrelor. Aspirin irreversibly inhibits COX1 and thereby blocks the production of thromboxane A 2, a vasoconstrictor and highly potent stimulant of platelet activation, leading to antiplatelet aggregation [31, 32]. Aspirin is the established first-line therapy in patients with STEMI, which specifically targets COX1 to exert its antiplatelet effect. However, monotherapy with aspirin still exposes patients to residual thrombotic risk in both acute and long-term phases. Therefore, the current guidelines emphasize dual antiplatelet therapy (DAPT), especially the widely use of P2Y12 inhibitors in oral antithrombotic management. Results from evidence-based medicine as confirmed that P2Y12 inhibitors combined with synergistic antiplatelet effect of aspirin can maximize the benefits of patients with STEMI, and it is the key to early and long-term drug treatment for patients with STEMI. Of note, owing to the recommendation of guideline [17] and DAPT-STEMI trial [33], short-term DAPT to 6 months was effective and beneficial to STEMI with high-bleeding risk population; therefore, in the review, it does not systematically discussed the choice of duration of DAPT use, but the optimal choice of oral antiplatelet therapy below.

Currently, the second-generation thienopyridine clopidogrel is the most widely used P2Y12 inhibitor. With the advent of large-scale clinical trials including CLARITY [34] and COMMIT [35], the combination use of clopidogrel and aspirin as standard treatment regimen has been the class I recommendation in the guidelines. However, studies have shown that in about 30–40% of the patients, especially those at high risk of bleeding, have platelet hyper-responsiveness during the course of clopidogrel treatment, which in turn leads to an increased risk of cardiovascular events [36, 37]. Therefore, how to optimize the use of oral antiplatelet agents to benefit patients with STEMI undergoing PPCI at high risk of bleeding is a problem we have faced in recent years.

Prasugrel is a third-generation thienopyridine. In the TRITON-TIMI 38 trial [38], patients ($n = 13{,}608$) with moderate-to-high-risk ACS scheduled for PCI were randomly assigned to receive either prasugrel or clopidogrel, in addition to aspirin. Prasugrel significantly reduced the primary efficacy endpoint (a composite of cardiovascular death, nonfatal MI, or nonfatal stroke) by 19% compared with clopidogrel over a median follow-up of 14.5 months, mainly driven by a reduction in nonfatal MI. Prasugrel also led to a significant 52% (HR, 0.52, $P < 0.001$) reduction in the rate of stent thrombosis, and a 34% (HR, 0.66, $P < 0.001$) decrease in the need for urgent target-vessel revascularization. Although this effect was hampered by significantly increased rates of major bleeding, the net clinical benefit was still in favor of prasugrel-treated patients. Prasugrel showed superior efficacy in major prespecified subgroups (age ≥ 75 years and cCr < 60 ml/min), without significant interactions between the characteristics of the patients and the treatment group. Besides, subgroup analysis of TRITON-TIMI 38 confirmed that prasugrel combined with aspirin was effective in reducing the risk of major endpoint events in STEMI patients undergoing PCI compared with clopidogrel combined with aspirin (6.5% vs 9.5%, HR 0.68, $P = 0.002$), and the key secondary endpoint of cardiovascular death, myocardial infarction, or urgent target vessel revascularization was also significantly reduced with prasugrel at 30 days (HR 0.75, $P = 0.02$) and 15 months (HR 0.79, $P = 0.02$) [39•, 40].

Ticagrelor is also a third-generation thienopyridine. The PLATO trial [41•] published in 2009 for ticagrelor showed that ticagrelor can consistently reduce the primary endpoint event (myocardial infarction, stroke, or cardiovascular death) at 1-year time point in patients with STEMI undergoing PPCI, as compared with clopidogrel (10.8% vs 9.4%; HR 0.87, $P = 0.07$). Ticagrelor reduced several secondary endpoints, including myocardial infarction alone (HR 0.80, $P = 0.03$), total mortality (HR 0.82, $P = 0.05$), and definite stent thrombosis (HR 0.66, $P = 0.03$) without increasing the risk of bleeding (HR 0.98, $P = 0.76$). In a post-hoc subgroup analysis [42••] of patients ($n = 4949$) with STEMI treated with PPCI within 12 h of admission, during a median of 286 days, major bleeding occurred in 6.7% in ticagrelor-treated patients versus 6.8% of clopidogrel-treated patients (HR 0.97, 95% CI 0.77 to 1.22, $P = 0.79$). The primary endpoint occurred in 7.9% of ticagrelor-treated patients versus 8.6% of clopidogrel-treated patients (HR 0.91, 95% CI 0.75 to 1.12, $P = 0.38$).

Treatment with ticagrelor versus clopidogrel reduced the occurrence of definite stent thrombosis (HR 0.58, 95% CI 0.37 to 0.89, $P = 0.013$). This evidence-based medicine confirmed that ticagrelor and prasugrel are more optimized long-term anticoagulant strategies. 2018 ESC STEMI guideline also recommends ticagrelor and prasugrel as a choice of postoperative medication for STEMI patients at high bleeding risk for PPCI.

Limitations

We acknowledge the following limitations to the review. First, we only searched for published studies and therefore the possibility of publication bias cannot be excluded. Second, we recognize that some relevant studies may have been missed as a result of our search criteria. Third, clinical trials so far often limit the inclusion of special populations, such as patient at high risk of bleeding, and the available data mentioned in the review come from subgroup analyses of clinical trials.

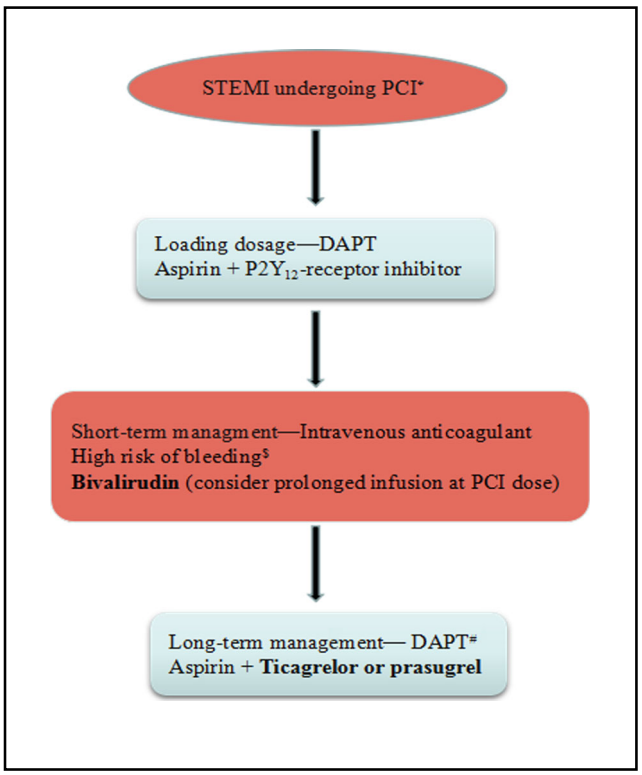

Fig. 1 Proposed algorithm for optimal antithrombotic therapy in patients with STEMI at high risk of bleeding undergoing PCI. Patients with STEMI at high risk of bleeding undergoing PCI are indicated by an asterisk sign. Inclusion criteria defined previously [13, 14] are indicated by a dollar sign. Continue DAPT to 6 months for patients at high risk of bleeding in accordance with guideline is indicated by a number sign. STEMI, ST-segment elevation myocardial infarction; PCI, primary percutaneous coronary; DAPT, dual antiplatelet therapy

Future Clinical Practice Guidelines

The clinical benefits of antithrombotic management for patients with STEMI and the choice of the optimal regimen remain uncertain in patients at high risk of bleeding, who need more careful evaluation and attention to anticoagulant management. To date, the highly anticipated multi-center, prospective clinical studies of EVOLVE short DAPT, MASTER DAPT, and POEM, targeting patients with high bleeding risk, are in the experimental stage.

Conclusion

Antithrombotic management plays a key role in both acute and long-term treatment of patients with STEMI. How to choose anticoagulant agents and antiplatelet agents to achieve individualized optimization in antithrombotic management is a top priority. Data from evidence-based medicine has confirmed that the use of intravenous anticoagulant agents in patients with STEMI during the implementation of PPCI is mandatory. For patients with STEMI undergoing PCI at high risk of bleeding, we believe that bivalirudin is the optimized intravenous anticoagulant agent based on the guideline recommendations and the subgroup analysis of the previous clinical data to improve prognosis or prevent stent re-thrombosis, oral dual antiplatelet agents are still the standard care of long-term antithrombotic therapy management. Currently, P2Y12 inhibitors mainly include clopidogrel, prasugrel, and ticagrelor. The effective combination application of ticagrelor or clopidogrel with aspirin, according to 2018 ESC STEMI guideline, can increase clinical benefit without increasing the risk of clinical bleeding. However, most of the clinical trials so far often limit the inclusion of special populations, such as patient at high risk of bleeding, and almost all clinical research data are from European and American. Therefore, we suggest large-scale, prospective, and randomized clinical trials to more objectively verify the optimal antithrombotic management strategies for people at high risk of bleeding (Fig. 1).

Funding Information The authors are funded by the National Natural Science Foundation Program of China (81700388, 81770386, and 399281570352), the Major Scientific Research Foundation of Colleges and Universities of Guangdong Province (2016KZDXM016), Frontier Research Program of Guangzhou Regenerative Medicine and Health Guangdong Laboratory (2018GZR110105001), and the Clinical Training Project Foundation of Southern Medical University (No. LC2016PY002).

Compliance with Ethical Standards

Conflict of Interest Yan Tu, Lu Hu, Chanjuan Yang, Arash Nemat, Gaopeng Xian, Jierong Zhang, and Qingchun Zeng declare 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.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):e78–140.
2.• Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119–77. **An important latest guideline for the management of acute myocardial infarction in patients presenting with ST-segment elevation.**
3. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541–619.
4. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013;34(10):719–28.
5. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004–13.
6. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med. 2007;357(24):2482–94.
7. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115(19):2549–69.
8. Michaels AD, Spinler SA, Leeper B, Ohman EM, Alexander KP, Newby LK, et al. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. Circulation. 2010;121(14):1664–82.
9. Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. Circ J. 2010;74(4):597–607.
10. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Nat Rev Cardiol. 2015;12(1):30–47.
11. Brummel KE, Paradis SG, Butenas S, Mann KG. Thrombin functions during tissue factor-induced blood coagulation. Blood. 2002;100(1):148–52.
12. Angiolillo DJ, Capodanno D, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J. 2010;31(1):17–28.
13. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J. 2007;28(16):1936–45.
14.•• Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015;373(21):2038–47. **An important randomized controlled study showing the definition of patient with STEMI at high risk of bleeding.**
15. Boneu B, Caranobe C, Cadroy Y, Dol F, Gabaig AM, Dupouy D, et al. Pharmacokinetic studies of standard unfractionated heparin, and low molecular weight heparins in the rabbit. Semin Thromb Hemost. 1988;14(1):18–27.
16. Palm M, Mattsson C. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. Thromb Haemost. 1987;58(3):932–5.
17. Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019 Jan 1;55(1):4–90.
18. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. Nat Rev Cardiol. 2017;14(6):361–79.
19. Fahrni G, Wolfrum M, De Maria GL, Banning AP, Benedetto U, Kharbanda RK. Prolonged high-dose bivalirudin infusion reduces major bleeding without increasing stent thrombosis in patients undergoing primary percutaneous coronary intervention: novel insights from an updated meta-analysis. J Am Heart Assoc. 2016;5(7).
20.•• Leonardi S, Frigoli E, Rothenbuhler M, Navarese E, Calabro P, Bellotti P, et al. Bivalirudin or unfractionated heparin in patients with acute coronary syndromes managed invasively with and without ST elevation (MATRIX): randomised controlled trial. BMJ. 2016;354:i4935. **An important randomized clinical trial confirming that the bivalirudin is the optimal intravenous anticoagulant therapy for patients with STEMI at high risk of bleeding based on the subgroup analysis.**
21. Lopes RD, Alexander KP, Manoukian SV, Bertrand ME, Feit F, White HD, et al. Advanced age, antithrombotic strategy, and bleeding in non-ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol. 2009;53(12):1021–30.
22. Erlinge D, Omerovic E, Frobert O, Linder R, Danielewicz M, Hamid M, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med. 2017;377(12):1132–42.
23. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet. 2014;384(9957):1849–58.
24. Muniz-Lozano A, Rollini F, Franchi F, Angiolillo DJ. Update on platelet glycoprotein IIb/IIIa inhibitors: recommendations for clinical practice. Ther Adv Cardiovasc Dis. 2013;7(4):197–213.
25. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. JAMA. 2005;293(14):1759–65.
26. Eitel I, Franke A, Schuler G, Thiele H. ST-segment resolution and prognosis after facilitated versus primary percutaneous coronary intervention in acute myocardial infarction: a meta-analysis. Clin Res Cardiol. 2010;99(1):1–11.
27. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med. 2008;358(21):2205–17.
28. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;358(21):2218–30.

29. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J. 2009;30(12):1457–66.
30. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. 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 from a multicentre, randomised controlled trial. Lancet. 2011;377(9784):2193–204.
31. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med. 2005;353(22):2373–83.
32. Capodanno D, Angiolillo DJ. Aspirin for primary cardiovascular risk prevention and beyond in diabetes mellitus. Circulation. 2016;134(20):1579–94.
33. Kedhi E, Fabris E, van der Ent M, Buszman P, von Birgelen C, Roolvink V, et al. Six months versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. BMJ. 2018;363:k3793.
34. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352(12):1179–89.
35. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005;366(9497):1607–21.
36. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Alfonso F, Macaya C, Bass TA, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol. 2007;49(14):1505–16.
37. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol. 2013;62(24):2261–73.
38. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357(20):2001–15.
39.• Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009;373(9665):723–31. **An important randomized clinical trial showing prasugrel is the superior oral antiplatelet drug for patients with STEMI at high risk of bleeding based on the analysis above.**
40. Udell JA, Braunwald E, Antman EM, Murphy SA, Montalescot G, Wiviott SD. Prasugrel versus clopidogrel in patients with ST-segment elevation myocardial infarction according to timing of percutaneous coronary intervention: a TRITON-TIMI 38 subgroup analysis (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38). J Am Coll Cardiol Intv. 2014;7(6):604–12.
41.• Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a platelet inhibition and patient outcomes (PLATO) trial subgroup analysis. Circulation. 2010;122(21):2131–41. **An important randomized clinical trial showing ticagrelor is the superior oral antiplatelet drug for patients with STEMI at high risk of bleeding based on the analysis above.**
42.•• Velders MA, Abtan J, Angiolillo DJ, Ardissino D, Harrington RA, Hellkamp A, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. Heart. 2016;102(8):617–25. **An important post-hoc subgroup analysis showing ticagrelor is the superior oral antiplatelet drug for patients with STEMI at high risk of bleeding**.