Cor et Vasa

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/crvasa

Přehledový článek | Review article

STEMI – The importance of balance between antithrombotic treatment and bleeding risk

Jan Pospíšil, Milan Hromádka, Ivo Bernat, Richard Rokyta

Kardiologické oddělení, Komplexní kardiovaskulární centrum, Lékařská fakulta Plzeň, Univerzita Karlova v Praze a Fakultní nemocnice Plzeň, Plzeň, Česká republika

INFORMACE O ČLÁNKU

Historie článku:
Došel do redakce: 30. 11. 2012
Přepracován: 14. 2. 2013
Přijat: 18. 2. 2013
Dostupný online: 24. 2. 2013

Keywords:
Antithrombotic treatment
Bleeding
ST elevation myocardial infarction

ABSTRACT

The incidence of ST elevation myocardial infarction (STEMI) is around 66 STEMI per 100,000 of population/year, with 6–12% hospital mortality in unselected patients [1]. Modern treatment strategies for STEMI are based on immediate antithrombotic treatment and primary percutaneous coronary intervention (PCI) with stent implantation. Therapy with combination of two or even three more potent antiplatelet and anticoagulant agents reduces both short-term and long-term ischemic risk, morbidity and mortality; on the other hand it is associated with higher risks of bleeding. The first part of this review is focused on the pathogenesis of thrombi in STEMI patients and antithrombotic drugs currently used to treat STEMI patients. In the second part we discuss several factors that can affect bleeding risks including the choice of access site for coronary angiography, prevention and treatment of bleeding in STEMI patients. Finding a balance which minimizes both thrombotic and bleeding risk is crucial, although it can be difficult and further randomized studies directed at finding this balance are needed.

Klíčová slova:
Antitrombotická léčba
Infarkt myokardu s elevacemi úseku ST
Krvácení

SOUHRN

Výskyt akutního infarktu myokardu s elevacemi úseku ST (STEMI) je zhruba 66 případů na 100 000 obyvatel za rok s 6–12% nemocniční úmrtností [1]. Moderní léčba pacientů se STEMI je založena na bezprostředním podání antitrombotických léků a primární koronární intervenci s implantací stentu. Léčba kombinací dvou či tří účinných antiagregačních a antikoagulačních léků snižuje krátkodobé i dlouhodobé riziko ischemických komplikací, morbiditu a mortalitu, na druhé straně je spojena s vyšším rizikem krvácení. První část přehledového článku je zaměřena na patogenezi trombózy a na aktuálně užívané antitrombotické léky v terapii pacientů se STEMI. Ve druhé části jsou diskutovány faktory ovlivňující riziko krvácení, což zahrnuje výběr místa tepenného přístupu ke koronarografii, prevenci a léčbu krvácení u pacientů se STEMI. Nalezení optimální strategie minimalizující jak riziko ischemických, tak krvácivých komplikací je zásadní a složité a je žádoucí provedení dalších randomizovaných studií zaměřených na tuto problematiku.

Adresa: MUDr. Milan Hromádka, Ph.D., Kardiologické oddělení, Komplexní kardiovaskulární centrum, Lékařská fakulta Plzeň, Univerzita Karlova v Praze a Fakultní nemocnice Plzeň, alej Svobody 80, 304 60 Plzeň-Lochotín, e-mail: hromadka@fnplzen.cz
DOI: 10.1016/j.crvasa.2013.02.004

Tento článek prosím citujte takto: J. Pospíšil et al., STEMI – The importance of balance between antithrombotic treatment and bleeding risk, Cor et Vasa 55 (2013) e135–e146, jak vyšel v online verzi *Cor et Vasa* na http://www.sciencedirect.com/science/article/pii/S0010865013000271

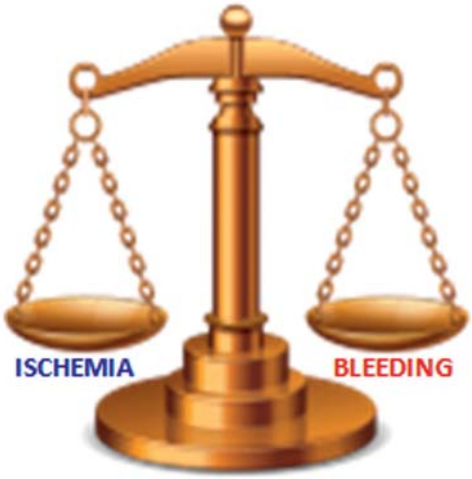

Fig. 1 – Delicate balance between ischemic and bleeding risk.

1 Introduction

Successful treatment of STEMI requires early diagnosis and urgent neutralization of lesion through antithrombotic therapy and mechanical revascularization. Modern antithrombotic treatment in conjunction with primary percutaneous coronary intervention (pPCI) has reduced morbidity and mortality in STEMI patients [2]. Nevertheless, effective treatment strategies may be associated with bleeding complications (Fig. 1). Depending on the study, the registry and the data source used, 3–14% of STEMI patients experience bleeding during the year following pPCI.

Bleeding in STEMI patients significantly prolongs intensive care unit stay and increases mortality [3]. According to the Thrombolysis In Myocardial Infarction (TIMI) bleeding criteria, TIMI major bleeding increases mortality 5 times and TIMI minor bleeding with transfusion increases the risks 2–3 times [4].

The efficacy, but also safety of antithrombotic drugs is crucial because today we use more potent antiplatelet agents and invasive strategies are now used to treat older patients with comorbidities as well as patients with higher risks of bleeding.

Current drug therapy in STEMI patients is based on evidence both from clinical trials in ACS with ST segment elevation and ACS without ST segment elevation or stable coronary artery disease (CAD), because many etiological and pathophysiological factors are similar. Therefore, in the part focused on antithrombotic drugs we discuss the results of trials across a broad spectrum of CAD (not only STEMI). In addition, we comment on experiences and trials from neurology and gastroenterology because these specialties have experience with the management of intracranial or gastrointestinal bleeding complications in patients on antithrombotic therapy. In summary, this review article focuses on current antithrombotic drugs, bleeding risks and complications in STEMI patients.

2 Pathogenesis of thrombi in STEMI

STEMI represents the most lethal form of acute coronary syndrome (ACS), in which a completely occlusive thrombus results in total cessation of coronary blood flow in the region of the infarct related artery and is associated with ST segment elevation on an electrocardiogram (ECG). The majority of myocardial infarctions (MIs) occur in patients with atherosclerotic stenosis associated with superimposed luminal thrombi. Arbustini et al. found coronary thrombi in 98% of patients dying from a clinically documented acute MI, and of those thrombi, 75% were caused by plaque rupture and 25% by plaque erosion [5].

Plaque rupture or erosion facilitates the interaction between inner plaque components and circulating blood. Tissue factor (TF) is a potent platelet activator and coagulation trigger. Recent research has provided a very detailed picture of the biochemical components and pathways involved in platelet activation.

At the site of a vascular lesion, circulating von Willebrand factor (vWF) binds to exposed collagen within the lesion, which subsequently binds to the glycoprotein IB/IX receptor on the membranes of platelets that are in the immediate vicinity, vWF is secreted from storage organelles in platelets and/or endothelial cells. Interaction of GP (glycoprotein) IB/IX – vWF is enough to promote binding of platelets to the subendothelium resulting in rapid accumulation of platelets in the site of lesion. GP VI binding to matrix collagen has slower binding kinetics, but when initiated, it promotes firm adhesion of platelet to the vessel surface.

Exposed matrix within a vessel wall and thrombin generated by activation of the coagulation cascade, as well as epinephrine and adenosine diphosphate are powerful platelet agonists. Each agonist stimulates the discharge of calcium and promotes the subsequent release of the platelet's granular content.

Adenosine diphosphate (ADP) released from platelet dense-granules as well as injured cells binds to the $P2Y_{12}$ receptors and then induces activation of the GP IIb/IIIa receptor and platelet aggregation. $P2Y_{12}$ plays a central role in amplification and stabilization of ADP-induced platelet aggregation.

Cyclooxygenase 1 (COX-1) is the key enzyme in prostaglandine biosynthesis. It converts free arachidonic acid, released from platelet membranes, to thromboxane A (TXA).

TXA further promotes platelet aggregation and is a potent vasoconstrictor. The initial recognition of a damaged vessel wall by platelets involves adhesion, activation and aggregation.

After the initial layer of platelets has spread over the lesion, additional platelets aggregate to form a secondary and tertiary layer of platelets (connection IIb/IIIa receptor–fibrin–IIb/IIIa receptor) and eventually form a white thrombus. In the final step there is recruitment of other cells, e.g. erythrocytes, neutrophils, monocytes, etc. [6].

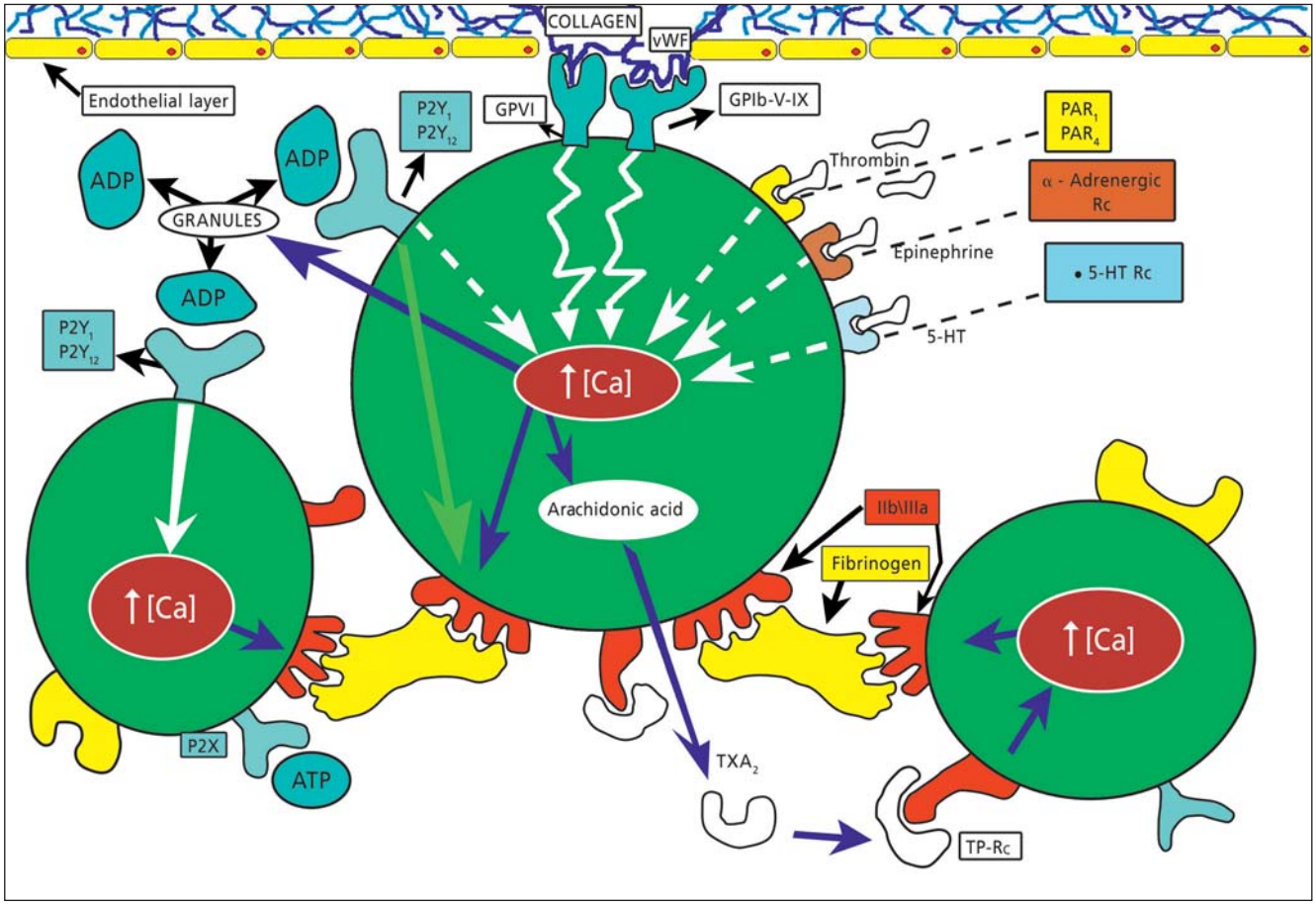

Fig. 2 – Mechanism of platelet adhesion, activation and aggregation [6].
ADP – adenosin diphosphate; ATP – adenosin triphosphate; GP – glycoprotein, 5-HT – 5 hydroxytriptamine; PAR – protease-activated receptor; Rc – receptor; TP-Rc – thromboxane receptor; TXA – thromboxane; vWF – von Willebrand factor.

3 Antithrombotic drugs

3.1 Classification of used antiplatelet agents (Fig. 2)

1. Aspirin blocks cyclo-oxygenase 1 (COX-1).
2. Platelet $P2Y_{12}$ blockers inhibit ADP receptors
   – ticlopidine, clopidogrel, prasugrel (irreversible inhibitors)
   – cangrelor and ticagrelor (reversible inhibitors).
3. Glycoprotein IIb/IIIa inhibitors block bridging of platelets by fibrinogen – abciximab, eptifibatide, tirofiban.
4. Thrombin receptor antagonist PAR (protease-activated receptor) – vorapaxar, atopaxar (currently tested in clinical trials).

The ESC guidelines for STEMI 2012 recommend aspirin + one of the newer $P2Y_{12}$ blockers (prasugrel or ticagrelor) preferred over clopidogrel [7].

3.1.1 Aspirin (acetylsalicylic acid)

Complete inhibition of platelet aggregation using aspirin usually requires a dosage of about 75 mg/day. It results in an inactive COX-1 enzyme for the remaining lifespan of the platelet (7–10 days). The restoration of normal platelet function, after aspirin administration, occurs only with the production of new platelets. One seventh of circulating platelets are renewed every 24 h; therefore, up to 30% of circulating platelets may show normal TXA_2 production after aspirin discontinuation for 48 h. Low dose aspirin does not affect the action of endothelial cell COX-1 and therefore does not reduce the production of PGI_2, which has many beneficial effects including potent antiplatelet effects.

A meta-analysis of 6 randomized trials (2427 patients with a history of myocardial infarction and 1757 patients with a history of transitory ischemic attack or stroke) showed that aspirin substantially reduces all-cause mortality by approximately 18% and nonfatal vascular events by 30% [8]. The optimal dose for efficacy and safety remains debatable. The results of CURRENT-OASIS 7 trial showed that in patients with ACS (25,086 patients studied, 29% STEMI and 71% non-STEMI or unstable angina pectoris), there was no significant difference after 30 days with regard to the primary outcome (cardiovascular death, MI, stroke) or major bleeding between the higher (300 mg daily) and lower (100 mg daily) dose aspirin groups. This finding was similar in the higher dose and lower dose clopidogrel groups [9].

Table 1 – TIMI bleeding classification [36].

Major	• Any intracranial hemorrhage • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL or a ≥ 15% absolute decrease in hematocrit • Fatal bleeding (bleeding that directly results in death within 7 days)
Minor	• Clinically overt (including imaging), resulting in hemoglobin drop of 3 to < 5 g/dL or ≥ 10% decrease in hematocrit • No observed blood loss: ≥ 4 g/dL decrease in the hemoglobin concentration or ≥ 12% decrease in hematocrit
Minimal	• Any clinically overt sign of hemorrhage (including imaging) associated with a < 3 g/dL decrease in hemoglobin concentration or < 9% decrease in hematocrit

TIMI – Thrombolysis In Myocardial Infarction.

Table 2 – Bleeding Academic Research Consortium (BARC) definition for bleeding [39].

Type 0	No bleeding
Type 1	• Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	• Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3
Type 3	Type 3a • Overt bleeding plus hemoglobin drop of 3–5 g/dL Type 3b • Overt bleeding plus hemoglobin drop > 5 g/dL • Cardiac tamponade • Bleeding requiring surgical intervention for control • Bleeding requiring intravenous vasoactive agents Type 3c • Intracranial hemorrhage
Type 4	CABG-related bleeding • Perioperative intracranial bleeding within 48 h • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of > 5 U whole blood or packed red blood cells within a 48-h period • Chest tube output > 2 L within a 24-h period
Type 5	Fatal bleeding

An analysis of an Italian trial (189,425 individuals from the general population taking low dose aspirin) by Berardis and colleagues showed the overall rate of major bleeding events per 1000 persons/year was 5.58 for aspirin users compared with 3.60 for non-aspirin users (incidence rate ratio 1.55 [95% CI, 1.48–1.63]) [10].

Continuing usage of low-dose aspirin after endoscopic treatment of a bleeding peptic ulcer (in patients with cardiovascular disease on aspirin) raises the risk of additional bleeding but may also reduce mortality rates, according to a report from Sung et al. Seventy-five patients with peptic ulcer bleeding were assigned to receive aspirin (80 mg/day) and 75 patients received a placebo for 8 weeks after endoscopic therapy. All subjects received intravenous pantoprazole (80 mg bolus, 8 mg/h for 72 h, followed by oral pantoprazole [40 mg/day] until the end of the study). The rate of recurrent ulcer bleeding at 30 days was nearly twice as high in the aspirin group compared to the placebo group: 10.3% vs. 5.4% ($p = 0.25$). However, the all-cause mortality rate at 8 weeks was much lower in the aspirin group: 1.3% vs. 12.9% ($p < 0.01$) due to the reduction of cardiovascular and cerebrovascular complications [11].

3.1.2 $P2Y_{12}$ receptor antagonists

The important role of the $P2Y_{12}$ receptor in platelet activation and thrombus formation has made it a crucial target in the management and prevention of arterial thrombosis.

Clopidogrel is an intestinally absorbed prodrug that is converted to its active metabolite in the liver by cytochrome P-450. It is estimated that approximately one third of clopidogrel-treated patients exhibit a diminished platelet response to clopidogrel. The results of the CURRENT-OASIS 7 trial in ACS patients showed a non-significant benefit of 150 mg/day over 75 mg/day clopidogrel in the whole population. However, a subgroup analysis showed a benefit from increased clopidogrel dose during the first week in ACS patients treated with PCI [12].

Is clopidogrel safer than aspirin with the respect of bleeding rate? The results of CAPRIE study (19,185 patients with atherosclerotic vascular disease that manifested either as a recent MI, ischemic stroke or symptomatic peripheral arterial disease) did not show significant differences in major bleeding between aspirin (300 mg/day) and clopidogrel (75 mg/day) group [13].

The MATCH trial (8600 patients with recent ischemic stroke or transient ischemic attack and at least one vascular risk factor) documented that the use of clopidogrel 75 mg + aspirin 75 mg caused more life-threatening bleeding than clopidogrel alone. At 18 months dual antiplatelet (DAPT) therapy increased life-threatening bleedings (2.6% vs. 1.3%); absolute risk increase 1.3 (95% CI 0.6–1.9). Major bleeding was also increased in the group receiving aspirin and clopidogrel but no difference was recorded in mortality [14].

The utility of tailored treatment with clopidogrel based on platelet function tests is now widely discussed.

The GRAVITAS study (2800 patients with ACS without ST segment elevation undergoing PCI and drug-eluting stent implantation) showed that although doubling the clopidogrel maintenance dose in poor responders may

improve the measured response, it does not necessarily improve outcomes [15]. In addition, the large clinical ARCTIC trial (2440 patients without STEMI, who were scheduled to undergo PCI with drug-eluting stents) did not confirm any significant improvements in clinical outcomes with platelet function monitoring and treatment adjustment for coronary stenting, compared with standard antiplatelet therapy without monitoring [16].

Genetic testing before starting clopidogrel therapy, in high-risk patients, and platelet function testing in those who suffer adverse events may facilitate the monitoring of clopidogrel treatment.

The possible interaction between clopidogrel and proton pump inhibitors is mentioned below (section on prevention of bleeding).

The next two drugs, prasugrel and ticagrelor are faster in action, more potent and more predictable than clopidogrel [17] and thus should be the preferred in combination with aspirin if not contraindicated.

Prasugrel is a pro-drug, its active metabolite appears in the circulation within 15 min of receiving a 60 mg loading dose [18]. In patients with documented CVD undergoing cardiac catheterization with PCI for angina pectoris, a 60 mg loading dose of prasugrel resulted in greater platelet inhibition than a 600 mg loading dose of clopidogrel [19]. Furthermore, a prasugrel maintenance dose of 10 mg/day results in more potent and consistent inhibition of platelet activation than a clopidogrel maintenance dose of 75 or 150 mg/day.

In the TRITON-TIMI 38 study, reduced rates of ischemic events (especially in diabetic or STEMI patients), including stent thrombosis in ACS patient undergoing PCI, were seen in prasugrel treated patients compared to the clopidogrel group. On the other hand, an increased rate of serious bleeding and fatal bleeding was also observed. Overall mortality did not differ between the two treatment groups [20].

In a subgroup of STEMI patients prasugrel and clopidogrel had similar safety profiles with respect to bleeding. Following 15 months of treatment, the rate of TIMI major and minor non-CABG bleeding in prasugrel and clopidogrel treated patients were comparable (5.1% vs. 4.7%, $p = 0.65$). Furthermore, prasugrel, compared with clopidogrel, did not significantly increase the rate of life-threatening bleeding (1.3 vs. 1.1%, respectively) [21].

The recommendation for discontinuing of prasugrel prior to cardiac surgery is 7 days. Prasugrel should not be administered to patients with a prior history of strokes or transient ischemic attacks. In patients aged > 75 years, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and the uncertain benefit; additionally, consideration should be given to lowering the maintenance dose to 5 mg in patients weighing < 60 kg.

In the TRILOGY trial, prasugrel failed to show a reduction in major cardiovascular events compared with clopidogrel in patients with acute coronary syndrome (ACS) with non-ST segment elevation and who were managed medically, i.e. without revascularization [22]. Interestingly, there were no differences (at the 30 months follow up) between the prasugrel and clopidogrel group in patients < 75 years and the overall population relative to rates of global use of strategies to open occluded coronary arteries (GUSTO); severe/life-threatening and TIMI major bleeding; and fatal and intracranial bleeding. A lower dose of prasugrel (5 mg) was used in those aged ≥ 75 years and in those weighing < 60 kg and appeared to be safe.

Ticagrelor is a nucleoside analog absorbed quickly from the gut and reaches peak concentration after 90 min. The drug plus its main metabolite are both pharmacologically active and are mainly excreted via bile and feces.

In the PLATO study (ticagrelor vs. clopidogrel), in patients with ACS, 7544 patients had STEMI. In these patients, a 13% reduction in the primary endpoint (incidence of MI, stroke or vascular death) was observed. There was no significant difference between the two trial arms with respect to any category of bleeding (major, minor, life-threatening, CABG or non-CABG related), except for the combination of no-procedure-related major and minor bleeding, which was more common with ticagrelor than with clopidogrel (5.1% vs. 3.7%) [23].

Contraindications for ticagrelor are a history of intracranial bleeding, as well as reduced liver function. Ticagrelor should be indicated with caution in patients with bradycardia or severe chronic obstructive pulmonary disease (COPD).

Cangrelor is parenteral $P2Y_{12}$ inhibitor with very short half-life; restoration of platelet function is observed within 60 min of drug discontinuation. This pharmacokinetic characteristic might be advantageous relative to urgent surgery. However, in the CHAMPION PCI study, cangrelor failed to show a benefit over clopidogrel [24,25].

3.1.3 Glycoprotein IIb/IIIa inhibitors

Abciximab, the most widely used agent from the glycoprotein (GP) IIb/IIIa inhibitors, is indicated as an addition to dual antiplatelet drug therapy (DAPT) in pPCI for the prevention of cardiac ischemic complications in patient with angiographic evidence of a large thrombus, TIMI flow 0–1, or other thrombotic complications, e.g. distal embolism [7].

The onset of abciximab effect (bolus dose) is less than 10 min. Its modification of platelet function lasts for up to 48 h after the infusion has been terminated, and low levels of GP IIb/IIIa receptor blockade are present for up to 15 days after the infusion is terminated.

In the STEMI–abciximab meta-analysis [26], major bleeding complications were higher with abciximab than placebo (4.7% vs. 4.1%; OR 1.16, $p = 0.36$), intracranial bleeding was the same.

Gu et al. studied 534 patients with STEMI and compared intracoronary (i.c.) abciximab to intravenous (i.v.) administration [27]. They found no difference relative to the combined endpoint of death, reinfarction or congestive heart failure. However, myocardial reperfusion, as assessed using myocardial blush and infarct size, were improved in the intracoronary group. Infarct size was similarly reduced, by about 30%, when measured using either creatine kinase-MB or cardiac troponin T. But cardiac enzyme was obtained in only 46% of patients. The incidence of in hospital major and minor bleeding was low and similar in both groups.

In meta-analysis from 8 randomized trials with 3259 patients by De Luca et al. [28] it was documented that

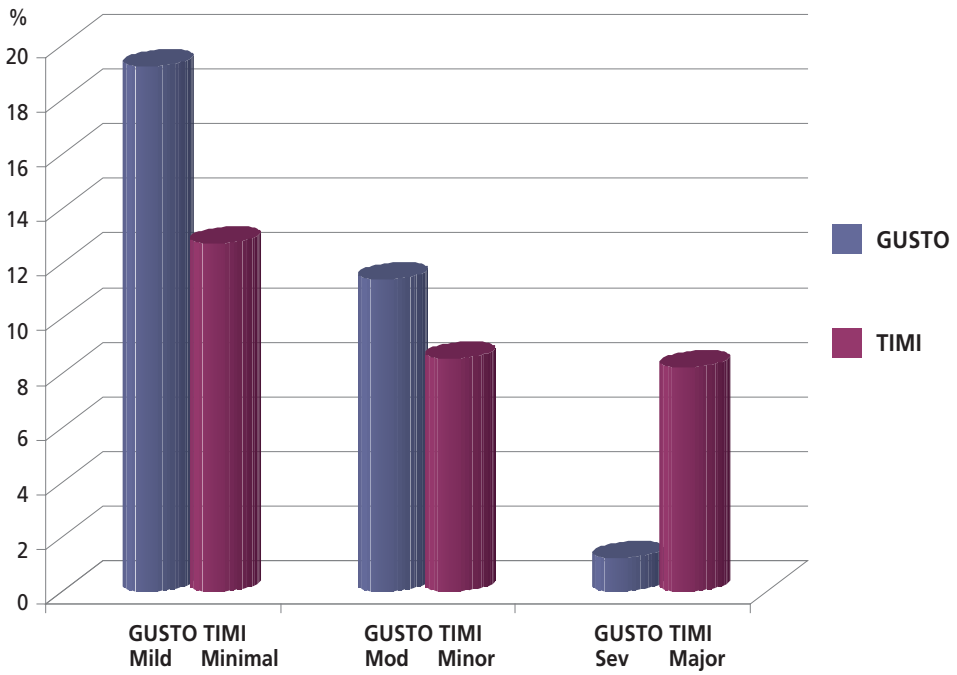

Fig. 3 – Bleeding incidence. Impact of bleeding definition [38]. N = 15,858 acute coronary syndrome patients from PURSUIT et PARAGON B. Mod – modest; Sev – severe.

i.c. administration of abciximab is associated with significant benefits in myocardial perfusion but not in clinical outcome at the short-term follow-up compared to i.v. abciximab administration, without any excess in major bleeding in STEMI patients undergoing pPCI.

The AIDA STEMI study [29] with 2065 patients compared i.c. vs. i.v. abciximab and found a similar rate for the primary composite clinical endpoint – death/MI/heart failure at 90 days (7.0% vs. 7.6%; OR [95% CI] 0.91 [0.64–1.28], p = 0.58). For death, the results showed non-significant difference (4.5% vs. 3.6%; OR 1.24 [0.78–1.97], p = 0.36). Reinfarction also did not differ between the treatment groups (1.8% vs. 1.8%; OR 1.0 [0.51–1.96], p = 0.99), whereas less patients in the intracoronary group had new congestive heart failure (2.4% vs. 4.1%; OR 0.57 [0.33–0.97], p = 0.04). Bleeding was not significantly different between i.v. vs. i.c. groups.

To date, there is no experience using combinations of abciximab and any of the newer antiplatelet agents, such as prasugrel or ticagrelor; however, such a coadministration could increase the risk of bleeding and therefore should be used with caution.

Eptifibatide is a peptide that reversibly binds to GP IIb/IIIa receptors. It has a very short half-life; as an example, four hours after cessation of infusion, patients have safely undergone CABG.

The large SCAAR registry (11,000 STEMI patients) suggests that eptifibatide is not inferior to abciximab in STEMI patients undergoing primary PCI with respect to the occurrence of death or MI at the 1 year follow up; this supports the use of either drug in clinical practice [30].

In patients after recent primary PCI with stent implantation, who require cessation of $P2Y_{12}$ before surgery, bridging with GP IIb/IIIa inhibitors appears effective in preventing adverse cardiac events; however, it may be associated with bleeding in patients undergoing cardiac surgery [31].

At the 3-year follow-up of the HORIZONS-AMI trial, eptifibatide and abciximab had comparable bleeding risks and clinical efficacy in patients after primary PCI [32].

3.2 Anticoagulants

In STEMI patients, 3 agents are recommended [7]:

1. Bivalirudin (level of evidence – LOE: IB)
2. Enoxaparin (LOE: IIbB)
3. Unfractionated heparin (should be used in patients not receiving bivalirudin or enoxaparin, LOE: IC)

The most frequent used anticoagulant in practice today is unfractionated heparin (UFH). It is a drug with long history, much experience and has an effective antidote (protamine). Bivalirudin is a specific and reversible direct thrombin inhibitor. In the HORIZONS-AMI study, the superiority of bivalirudin was demonstrated over a combination of UFH + abciximab. This study reported reduction in all cause and cardiovascular (CV) mortality at 30 days up to 3 years, and the risk of bleeding was also reduced [33].

In a retrospective study of 900 US patients, bivalirudin was compared to heparin (without GP IIb/IIIa inhibitors). The results confirmed a similar safety and efficacy profile for both drugs [34].

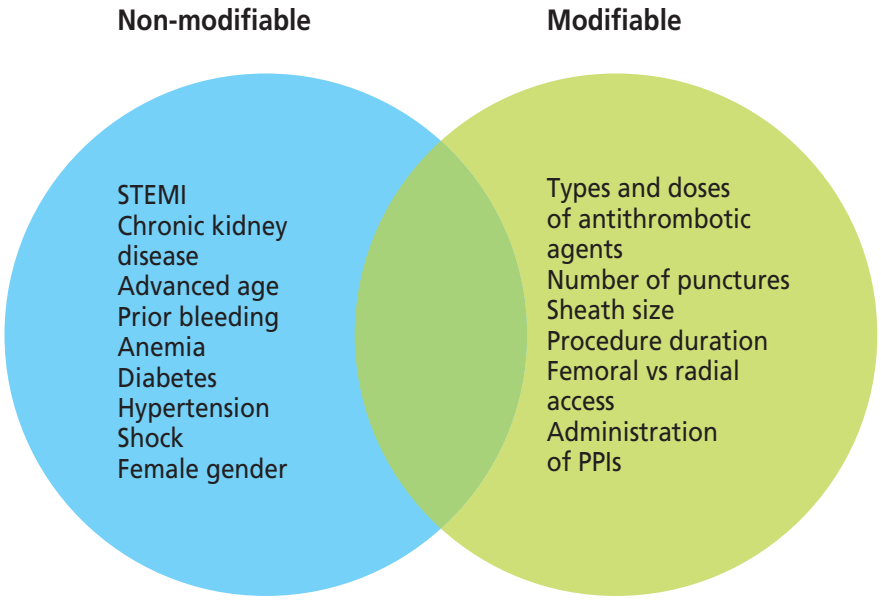

Fig. 4 – Predictors of bleeding.
PPI – proton pump inhibitor.

Enoxaparin is recommended as an alternative to UFH or bivalirudin. Comparison of enoxaparin vs. UFH in the ATOLL study showed that enoxaparin reduced the combined ischemic endpoint of death, reinfarction or urgent revascularization (8.5% vs. 5.1%, $p = 0.04$). The incidence of major bleeding did not differ between groups (5% vs. 5%; $p = 0.79$) [35].

4 Bleeding scores and predictors

Bleeding events are important endpoints for the assessment of drugs and safety profiles during randomized trials. There are many data from several trials relative to bleeding, but unfortunately, to date, there has been a lot of non-homogeneity regarding the definition of bleeding and its categorization (i.e. minor, moderate, major, life-threatening, severe, serious, with need of transfusion, etc.) and many different classifications are used, e.g. TIMI [36] (Table 1), GUSTO [37], STEEPLE, GRACE, PLATO etc. Therefore, it is difficult to compare results between trials (Fig. 3) [38]. In 2010, academic research on bleeding and drug administration developed new a universal bleeding classification for cardiovascular clinical trials, called the BARC classification [39], which consists of 5 types of bleeding (Table 2).

Rates of bleeding complications have been steadily dropping after elective percutaneous coronary interventions according to registry data published in May 2012 [40]. However, the decrease was not seen in STEMI patients.

Based on the results from many studies, several important predictors of bleeding are known (Fig. 4). The most common is age; other strong predictors are shock, use of anticoagulant treatment and/or NSAIDs, prior history of bleeding, renal failure, comorbidities (sepsis and mechanical ventilation and diabetes mellitus). Other predictive factors include: low body weight, obesity, anemia and female gender. Moreover, antithrombotic treatment strategies (e.g. the use of GP IIb/IIIa inhibitors) also play an important role [41].

The relationship between bleeding and mortality is both direct and indirect. Intracranial and gastrointestinal hemorrhages are well recognized as potentially fatal events. However, consequences of bleeding may have other detrimental effects:

(1) Interactions between activated platelets and clotting cascade produce a rapid hemostatic response at site of vascular injury and deficiency of an antithrombotic protective mechanism.
(2) Further, procoagulation factor i.e., increased erythropoietin synthesis in response to anemia caused by bleeding. Systemic prothrombotic states might last beyond the acute phase, by causing platelet activation and inducing plasminogen activator inhibitor-1 synthesis [42].
(3) In the presence of severe bleeding antithrombotic medication is almost always withdrawn or reduced at least temporarily.
(4) Finally, the use of transfusions has prothrombotic effects and increases mortality in STEMI patients [43].

A meta-analysis of the REPLACE-2, ACUITY and HORIZONS-AMI trials performed by Mehran et al. showed that non-CABG related bleeding within 30 days was strongly associated with an increased risk of 1 year mortality in patients undergoing PCI for all indications [4].

5 Source of bleeding after STEMI

Post-STEMI bleeding is divided into access site (40–50%) and non-access site bleeding (50–60%). As mentioned earlier, the ratio between access site and non-access site bleeding found in different studies varies depending on the bleeding classification used. Several factors appear to influence the reported rate of bleeding complications in clinical trials, including: (1) population inclusion/exclusion criteria, (2) rate and type of invasive procedures, (3) bleeding definition, and (4) antithrombotic agents used [44].

5.1 Non-access site bleeding

The gastrointestinal (GI) tract is the most common non-access site bleeding (1 year incidence 0.7–3.5%). The greatest risk is previous GI bleeding. The majority of bleeding is in upper GI tract (ulcer or erosion of stomach, duodenum and esophagus). Prevention and treatment are discussed below.

Intracranial bleeding (0.1–0.4%) is the most serious location of bleeding. In the thrombolytic era, the incidence of intracranial bleeding between streptokinase vs. alteplase treated patients was 0.5% vs. 0.7%, $p = 0.03$ (GUSTO trial) [37].

In the era of primary PCI, the incidence of intracranial bleeding has dropped below 0.4% per 1 year for STEMI. In intracranial bleeding, immediate withdrawal and antagonization of the antithrombotic drug is mandatory and close cooperation with the neurosurgeon is needed.

Urogenital bleeding (0.5–1.5%) is usually temporary and not associated with the need for a blood transfusion or surgical intervention.

Occasionally one can see bleeding in respiratory tract or significant drops of hemoglobin without a clinically proven bleeding site.

Retroperitoneal bleeding (which can be difficult to diagnose) is pure non-access bleeding when other than femoral approach for coronary catheterization and intervention is used.

5.2 Access site bleeding

Puncture site for the primary PCI is the most frequent source of bleeding. These complications in clinical practice include large hematomas in the groin, arterio-venous (AV) fistulas, aneurysms and pseudoaneurysms of artery or retroperitoneal bleeding. Fortunately, these complications may be substantially reduced when the radial approach is used in an experienced center. Although the radial artery is superficial and hemostasis can be achieved easily, access site bleeding can occur that, if left unchecked, can lead to forearm hematoma and rarely, to compartment syndrome [45].

In case of femoral approach the use of closure device may be considered. However, studies have not shown a significant benefit in terms of a reduction in access site complications, including bleeding risks. The main advantage of closure devices is that they are more comfortable for patients.

Jolly et al. in 2009 documented the benefit of the radial vs. femoral approach in the first large meta-analysis on the subject [46]. They reviewed 13 studies and 1958 STEMI patients who had been randomized to trans-radial approach (TRA) vs. trans-femoral approach (TFA). This analysis showed a remarkable and highly significant 73% reduction of major bleeding complications in the TRA arm. Interestingly, this dramatic reduction of major bleeding complications was also associated with a trend toward fewer deaths, myocardial infarctions, and strokes (OR 0.71; 95% CI, 0.4 –1.01; $p = 0.06$) in TRA compared to the TFA group.

The benefit of TRA over TFA (both lower morbidity and cardiac mortality) was subsequently documented in a meta-analysis by Mamas et al. [47]. The researchers chose 9 studies from 2003 to 2011 and included a total of 2977 STEMI patients. Within the studies, 1460 patients underwent transradial PCI and 1517 patients had transfemoral PCI. Patients with the TRA had a 45% relative reduction in major bleeding; additionally, a 70% reduction in access site complications and 48% relative reduction in mortality were found.

The next meta-analysis, comparing the radial and femoral approach in primary PCI for STEMI was published by Joyal et al. [48]. The study included 10 trials involving 3347 patients. The inclusion criteria were a randomized study design, a patient with documented STEMI undergoing primary PCI, a control group undergoing femoral access, and the type of clinical outcome (death, major bleeding, vascular complications, or hematoma), and

Table 3 – Managing bleeding in patients on anticoagulants and antiplatelets [57].

Medication	Treatment
Aspirin, $P2Y_{12}$ inhibitor	Transfuse platelets to raise count by 50,000/μl
Glycoprotein IIb/IIIa inhibitor	Stop infusion of abciximab if given, transfuse platelets to raise count by 50,000/μl
Warfarin	• If INR is 5–9 and no bleeding, discontinue warfarin, consider vitamin K and recheck INR within 24 h • If INR is > 9 and no bleeding, discontinue warfarin, give 5 mg oral vitamin K and recheck INR within 24 h • If major bleeding is present, administer 3–5 units FFP and 10 mg vitamin K (subcutaneus) or slow intravenous infusion • If INR is < 5 and no bleeding, stop warfarin and recheck INR within 24 h
Enoxaparin	Protamine may be effective. Dose 1 mg protamin per 1 mg enoxaparin
Heparin	1 mg protamin i.v. per every 100 units heparin given over previous 4 h (to maximum 50 mg)

FFP – fresh frozen plasma; INR – international normalized ratio.

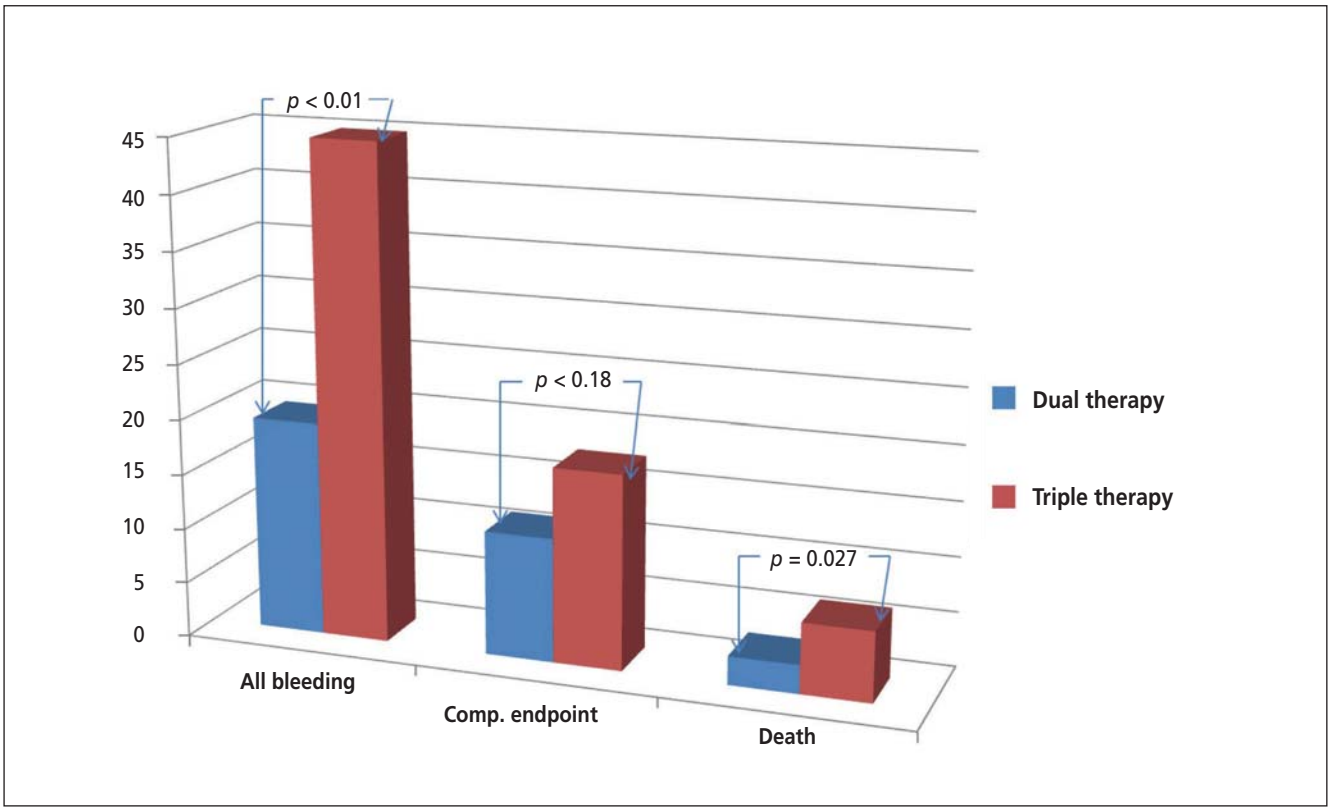

Fig. 5 – WOEST trial. 1 year results. Composite endpoint stroke, myocardial infarction, death, stent thrombosis, target vessel revascularization [55].

procedure time. The radial approach was associated with improved survival (OR 0.53; 95% CI, 0.33–0.84, p = 0.93) and reduced vascular complications/hematoma (OR 0.35; 95% CI, 0.24–0.53, p = 0.66). A non-significant trend was found toward reduced major bleeding using the radial approach (OR 0.63; 95% CI, 0.35–1.12, p = 0.79)

The RIVAL trial randomized patients with ACS into intervention by femoral approach vs. the radial approach. In the STEMI subgroup (1958 patients), the authors found a statistically significant reduction in primary endpoint (death, MI, stroke and non-CABG bleeding) and non-significant difference in non-CABG major bleeding (according to OASIS bleeding classification) [49].

The RIFLE STEACS trial (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) was a multicenter, randomized, parallel-group study with 1001 acute STEMI patients undergoing primary/rescue percutaneous coronary intervention. Patients were randomized into the radial (n = 500) or femoral (n = 501) approach between 2009 and 2011 [50]. Romagnoli et al. reported a significant reduction in primary endpoint, i.e. 30 day rate of net adverse clinical events (NACE = composite of cardiac death, stroke, myocardial infarction, target lesion revascularization, and bleeding at 30 days): 13.6% in the radial access group vs. 21.0% in the femoral (p = 0.003). Radial access was associated with significantly lower cardiac mortality (5.2% vs. 9.2%, p = 0.02) and bleeding (7.8% vs. 12.2%, p = 0.026). Non-access site bleeding did not differ between groups, but significant reduction (62%) of access site bleeding was documented in the radial access group.

Based on the results of the RIVAL-STEMI substudy and the RIFLE STEACS study, the ESC 2012 guidelines for STEMI recommend the preference of radial access over femoral access for primary PCI (level of recommendation IIaB), if the procedure is performed by experienced radial operator.

6 Prevention of bleeding

The predictors of bleeding are known (see above), but a specific risk score for STEMI patients regarding a rapid estimation of bleeding risk has not yet been developed. In 2009 the CRUSADE Bleeding Score, for prediction of in hospital bleeding, was created for NSTEMI patients [51]. The preference of radial access and/or smaller access sheath size for coronary catheterization in experienced centers has been already mentioned. Care of the puncture site after the intervention is also of importance. For hemostasis, many radial compression devices exist, for example: Hemostop (Zoom Co. Medic), RadiStop (Radi Medical Systems), RadStat (Merit Medical Systems), TR Band (Terumo) [52].

Based on an evaluation of both thrombotic and bleeding risk, tailored treatment strategies should be used for every patient. One should take into account the age and weight of the patient, renal function, etc. Moreover, the proper dose and dose adjustment of antithrombotic drugs is needed and one should avoid combinations of antithrombotic drugs without proven efficacy and safety.

In the current era, this is of the most importance, since both novel antiplatelet drugs (ticagrelor, prasugrel) and anticoagulants (factors Xa inhibitors – rivaroxaban, apixaban and thrombin inhibitors – dabigatran) are administered in the treatment of ACS patients and patients with atrial fibrillation respectively, but their combinations have not been tested in clinical trials yet.

One of the most frequent non-access site bleeding complications is bleeding from a gastroduodenal ulcer and/or erosions. In recent years, possible interactions between proton pump inhibitors (PPI, namely omeprazole) and clopidogrel (possibly resulting in reduced clopidogrel effect) have been discussed. Although laboratory proven, the interaction between clopidogrel and omeprazole has not been shown to increase cardiovascular risks with drug coadministration in patients with ACS, whereas a significant reduction in gastrointestinal bleeding with PPIs use was observed [53]. The retrospective CALIBER study (UK, 2012) included 24,471 patients with ACS. Patients were prescribed clopidogrel and aspirin and 12, 439 (50%) also PPI. The interaction between the PPI and clopidogrel was not clinically important [54]. Therefore, concurrent clopidogrel and PPI use (with the possible preference of pantoprazole) appears safe, but co-prescription is recommended only for patients at risk for gastrointestinal complications.

Novel $P2Y_{12}$ blockers (ticagrelor, prasugrel) do not have any interactions with PPI, are more efficient than clopidogrel, but this also suggests a need for more widespread PPI use during DAPT (or triple antithrombotic therapy). Based on ESC 2012 STEMI guidelines, PPI should be considered for patients with a history of GI bleeding and are appropriate for patients with multiple risk factors, such as advanced age, anticoagulation, steroids, NSAIDs. H2 blockers are insufficient in prevention (5 times weaker than PPI for upper GI bleeding prevention).

There are several specific patient subgroups for higher risks of bleeding, e.g. patients with renal insufficiency or patients undergoing surgery. In addition, difficult clinical scenarios can occur when STEMI patients also require long-term anticoagulation, i.e. patient with mechanical valve or atrial fibrillation with CHA_2DS_2-VASc score ≥ 1. In these patients, there are both high thrombotic (intracardiac thrombi or stent thrombosis) and bleeding risks, which may be estimated using the HAS-BLED score, it is preferable to implant a bare-metal stent instead of drug-eluting stent unless the latter is absolutely indicated. The second point is the strategy of long-term post-PCI antithrombotic treatment. When anticoagulant treatment is indicated, it cannot be replaced by antiplatelet agents; therefore the dilemma is the type and duration of antiplatelet therapy. Higher HAS-BLED score (≥ 3 points) does not necessarily indicate antithrombotic treatment cessation, but clinicians should be very careful and intensify monitoring for bleeding occurrences.

Current ESC guidelines recommend triple therapy (oral anticoagulant + aspirin + clopidogrel) and the duration of DAPT is based on the type of stent and type of the event (i.e. elective PCI vs. PCI in ACS). It is well known, that this triple therapy is associated with significantly higher bleeding risks. The recently published WOEST trial compared OAC + DAPT (aspirin + clopidogrel) vs. oral anticoagulant + clopidogrel (without aspirin) [55]. Approximately one third of the patient population had ACS. The authors observed significantly higher incidences of bleeding in triple therapy group and interestingly also higher mortality and combined endpoint at 12 months in the triple therapy group (Fig. 5). Further and larger studies are clearly needed with this specific patient population. At present, triple therapy with oral anticoagulant + aspirin + prasugrel or ticagrelor is not recommended since it might increase the risk of bleeding.

The most frequent reason for $P2Y_{12}$ inhibitors and/or aspirin cessation is surgery, bleeding and non-compliance of the patient with treatment. Dual antiplatelet therapy is recommended for 12 months after STEMI events. During this period the patient may require planned or urgent non-cardiac surgical procedures. Antiplatelet therapy maintenance or withdrawal in these scenarios is not based on evidence, but on expert opinion taking into account the bleeding risk of the procedure and time after STEMI. Duration of stent endotelisation is in detail discussed in chapter 7. At this point we will summarize briefly our local strategy, which is based on the data from literature [56,57].

(1) Patients on aspirin monotherapy (usually longer than 12 months after a STEMI event).
Prior to surgery, aspirin can be continued without interruption, with the exception of intracranial and selected ophthalmic surgery, where aspirin should be discontinued 7 days prior to surgery.
(2) Patients on dual antiplatelet therapy (DAPT).
a) High risk situations (bare-metal stent [BMS] placement within the previous 12 weeks and drug-eluting stent [DES] implanted within previous 6–12 months, anytime in patients with a history of stent thrombosis, stent in left main coronary artery and/or last patent coronary artery or coronary artery bypass, etc.)
Postpone the surgery if possible. If the surgery is mandatory, DAPT should be continued. Only 6–12 months after BMS implantation (when the benefits of early operations prevail) or in cases of neurosurgical/selected ophthalmological procedures maintain aspirin and withdraw the $P2Y_{12}$ blocker 7 days before surgery.
b) Low risk situations (not fulfilling criteria 2a).

Before the majority of surgical procedures, aspirin should be continued and the $P2Y_{12}$ blocker withdrawn 7 days before surgery. In dental procedures, DAPT is maintained. In patients undergoing intracranial and selected ophthalmic surgery, withdrawal of DAPT should be considered (at least the $P2Y_{12}$ blocker).

Management of all above mentioned situations require a close multidisciplinary approach (cardiologist, anesthesiologist and surgeon) in the pre-, peri- and postoperative period.

7 Treatment of bleeding and discontinuation of antiplatelet therapy

The treatment of clinically significant bleeding is primarily based on attempts to control the source of bleeding.

In access site bleeding after pPCI it is necessary to extract the femoral sheath with subsequent careful compression. For severe gastrointestinal bleeding it is an early endoscopic exam and treatment, i.e. PPI in continual i.v. infusion in doses of 8 mg/h for the first 3 days. With respect to a temporary withdrawal of antiplatelet drugs (aspirin or $P2Y_{12}$ antagonist or both), the optimal strategy in patients on DAPT and peptic ulcer bleeding remains to be determined and should be tailored to every patient.

If there is a suspicion of intracranial bleeding, a CT scan is urgently indicated and after confirmation of a brain hemorrhage, consultation with neurosurgery is required. If there is urethral bleeding, then the insertion of urethral 3 way catheter is needed.

In life-threatening bleeding, the immediate discontinuation and eventually antagonism of antiplatelet therapy is indicated (antidotes – see Table 3) [57].

Administration of a transfusion and/or platelets must be reserved for only serious bleeding with circulatory instability, because inappropriate transfusion of red cells worsens the prognosis. Premature discontinuation of antiplatelet therapy may be at the cost of increased incidences of cardiovascular mortality and morbidity [58].

In an Italian study [59] with 1358 patients (STEMI 30%) after PCI + drug-eluting stent (sirolimus-eluting stent 707 patients and paclitaxel-eluting stent 651 patients), early discontinuation of clopidogrel and/or aspirin (in the first month) significantly increased the rate of stent thrombosis (7.6 % vs. 3.4 %, $p = 0.038$), MACE (28.6 % vs. 13.7 %, $p < 0.001$) and cardiovascular death (5 % vs. 1.2 %, $p < 0.007$).

Premature discontinuation of dual antiplatelet treatment is strongly associated with stent thrombosis, which may manifest as STEMI, malignant arrhythmias or even sudden death [60]. Stent thrombosis is a platelet mediated process that occurs through progressive platelet activation and aggregation ultimately leading to thrombus formation. PCI causes endothelial and tunica media damage that heals via neointimal formation. This process usually lasts up to 6–12 weeks with bare-metal stents (BMS) and up to 6–12 months with drug-eluting stents [61]. It seems that time to endothelization will be decreased with the newest generations of DES, either second generation, or DES with bioresorbable polymers and fully bioresorbable stents [62]. Hopefully, the recommended duration of DAPT after STEMI events can be shortened. In December 2013 we expect results from the DAPT STEMI study [63] – a randomized, open label trial of 6 months vs. 12 months with dual antiaggregation therapy (aspirin + prasugrel or ticagrelor) after pPCI + drug-eluting stent. Discontinuation of aspirin increases risk of CV morbidity and mortality in patients with cardiovascular comorbidities. A retrospective trial from Sweden with 118 patients after aspirin discontinuation documented that 44 of 118 patients (37%) either died or developed acute cardiovascular events. It means that patients with cardiovascular comorbidities who stop low-dose aspirin therapy had an almost 7-fold increased risk for death or acute cardiovascular events (hazard ratio, 6.9; 95% confidence interval, 1.4–34.8) compared to patients continuing this therapy during the first 6 months of the follow-up period. On the contrary, such an association was not observed among patients without cardiovascular comorbidities [64].

8 Future

Although prasugrel and ticagrelor act more quickly than clopidogrel, there remains a need for an affective intravenous formulation of a $P2Y_{12}$ blocker in patients before surgical intervention, patients with impossible or impaired gut absorption (e.g. after cardiopulmonary resuscitation, cardiogenic shock, mechanical ventilation with deep sedation, etc.). It is also important to have agents that are rapidly reversible in patients awaiting surgical intervention.

New agents (e.g. vorapaxar) are in development. There is also a place for testing new combinations of drugs. The BRAVE-4 study (prasugrel + bivalirudin vs. UFH + clopidogrel) is under way. The question is whether aspirin will remain an indispensable part of antiplatelet therapy in the era of newer, more potent $P2Y_{12}$ inhibitors and if novel anticoagulants can be combined with other antiplatelet agents. Recent developments in catheters and closure devices have opened other fields regarding improvements in primary PCI results with reduced risks of bleeding.

Last but not least, genetic testing will be probably used more widely in clinical practice as a method of individualizing patient care.

9 Conclusion

Patients with acute myocardial infarction with ST segment elevation are indicated for combined anticoagulant and dual antiplatelet treatment as soon as possible after establishing the diagnosis with subsequent early primary PCI with stent implantation. Dual antiplatelet therapy is then administered usually for one year. This strategy, which reduces immediate and long-term ischemic risks, carries a higher short-term and long-term risk of bleeding, which is a very important predictor of morbidity and mortality. The preference of radial access in centers experienced with the procedure significantly reduced bleeding complications and improved clinical outcomes in STEMI patients. After individual stratification of thrombotic and bleeding risks one should apply measures to reduce the risk of these complications using effective and safe combinations of antiplatelet and anticoagulant agents while minimizing the risks of bleeding. Similarly, when bleeding occurs, a tailored treatment approach should be applied for each individual patient.

Acknowledgements

Supported by the Charles University Research Fund (project number P36) and the project Ministry of Health, Czech Republic for conceptual development of research organization 00669806 – Faculty Hospital in Pilsen.

References

[1] P. Widimský, P. Kala, R. Rokyta, Summary of the 2012 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST elevations, Cor et Vasa 54 (2012) e273–e289.

[2] T.W. Johnson, J.W. Strange, V. Oriolo, et al., Collected resources: percutaneous intervention, Heart 98 (2012) 74–75.

[3] S.V. Rao, O. Grady, K.S. Pieper, et al., Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes, American Journal of Cardiology 96 (2005) 1200–1206.

[4] R. Mehran, S. Pocock, E. Nikolsky, et al., Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials, Journal of the American College of Cardiology. Cardiovascular Interventions 4 (2011) 654–664.

[5] E.D. Arbustini, B. Dal Bello, P. Morbini, et al., Plague erosion is a major substrate for coronary thrombosis in acute myocardial infarction, Heart 82 (1999) 269–272.

[6] J.J. Badimon, B. Ibanez, V. Fuster, et al., Coronary thrombosis local and systematic factors, in: V. Fuster, R.A. Walsh, R.A. Harrington, et al., Hurt's The Heart, 13th edition, 2011, pp. 1225–1227.

[7] Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), P.G. Steg, S.K. James, D. Atar, et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, European Heart Journal 33 (2012) 2569–2619.

[8] S.M. Weisman, D.Y. Graham, Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events, Archives of Internal Medicine 162 (2002) 2197–2202.

[9] R.S. Mehta, J.F. Tanguay, J.W. Eikelboom, et al., Double--dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7), Lancet 376 (2010) 1233–1243.

[10] G. De Berardis, G. Lucisano, A. D'Ettorre, et al., Association of aspirin use with major bleeding in patients with and without diabetes, The Journal of the American Medical Association 307 (2012) 2286–2294.

[11] J.J. Sung, J.Y. Lau, J.Y. Ching, et al., Continuation of low--dose aspirin therapy in peptic ulcer bleeding: a randomized trial, Annals of Internal Medicine 152 (2010) 1–9.

[12] S. Mehta, J.P. Bassand, S. Chrolavicius, et al., The CURRENT--OASIS 7, The New England Journal of Medicine 363 (2010) 930–942.

[13] CAPRIE Steering Commitee, A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE), Lancet 348 (1996) 1329–1339.

[14] H.C. Diener, J. Bogousslavsky, L.M. Brass, et al., Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH), Lancet 367 (2004) 331–337.

[15] M.J. Price, D. J. Angiolillo, P. Teirstein, et al., Platelet reactivity and cardiovascular outcomes after percutaneous coronary intervention: a time-dependent analysis of the Gauging Responsiveness with a VerifyNow P2Y12 assay: Impact on Thrombosis and Safety (GRAVITAS) trial, Circulation 124 (2011) 1132–1137.

[16] J P. Collet, G. Cayla, T. Guisset, et al., Randomized comparison of platelet function monitoring to adjust antiplatelet therapy versus standard of care: (ARCTIC) study, American Heart Journal 161 (2001) 5–12.

[17] P. Widimsky, J.W. Jukema, B. Meier, et al., Evolving strategies in the management of acute coronary syndromes with oral antiplatelet agents, Cor et Vasa 54 (2012) e32–e38.

[18] K.I. Kallirroi, M.E. Tsoumani, A. Ioannis, et al., Pharmacodynamic properties of antiplatelet agents, current knowledge and future perspectives, Expert Review of Clinical Pharmacology 5 (2012) 319–336.

[19] S.D. Wiviott, D. Trenk, A.L. Frelinger, et al., Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 trial, Circulation 116 (2007) 2923–2932.

[20] S.D. Wiviott, E. Braunwald, H. Carolyn, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, The New England Journal of Medicine 357 (2007) 2001–2015.

[21] M.J. Price, J.S. Walder, B.A. Baker, et al., Recovery of platelet function after discontinuation of prasugrel or clopidogrel maintenance dosing in aspirin-treated patients with stable coronary disease: the RECOVERY trial, Journal of the American College of Cardiology 59 (2012) 2338–2343.

[22] M.T. Roe, P.W. Armstrong, K.A. Fox, et al., Prasugrel versus clopidogrel for acute coronary syndromes without revascularization, The New England Journal of Medicine 367 (2012) 1297–1309.

[23] P.G. Steg, S. James, A. Robert, et al., A Platelet Inhibition and Patient Outcomes (PLATO) Trial subgroup analysis, Circulation 122 (2010) 2131–2141.

[24] R.A. Harrington, G.W. Stone, S. McNultz, et al., Platelet inhibition with cangrelor in patients undergoing PCI, The New England Journal of Medicine 361 (2009) 2318–2329.

[25] D.L. Bhatt, A.M. Lincoff, C.M. Gibson, et al., Intravenous platelet blockade with cangrelor during PCI, The New England Journal of Medicine 361 (2009) 2330–2341.

[26] G. De Luca, H. Suryapranata, G.W. Stone, et al., Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials, The Journal of the American Medical Association 293 (2005) 1759–1765.

[27] Y.L. Gu, M.A. Kampinga, W.G. Wieringa, 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 122 (2010) 2709–2717.

[28] G. De Luca, M. Verdola, H. Suryapranta, et al., Benefits from intracoronary as compared to intravenous abciximab administration for STEMI patients undergoing primary angioplasty: a meta-analysis of 8 randomized trials, Atherosclerosis 222 (2012) 426–433.

[29] H. Thiele, J. Wöhrle, R. Hambrecht, et al., Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial, Lancet 379 (2012) 923–931.

[30] A. Åkerblom, S.K. James, M. Koutouzis, et al., Eptifibatide is noninferior to abciximab in primary percutaneous coronary intervention: results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry), Journal of the American College of Cardiology 56 (2010) 476–478.

[31] T. Ben Morrison, B.M. Horst, M.J. Brown, et al., Bridging with glycoprotein IIb/IIIa inhibitors for periprocedural management of antiplatelet therapy in patients with drug eluting stents, Catheterization and Cardiovascular Interventions 79 (2012) 575–582.

[32] W. S. Gregg, W. Bernhard, G. Guagliumi, et al, The HORIZONS--AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction, The New England Journal of Medicine 358 (2008) 2218–2230.

[33] G.W. Stone, B. Witzenbichler, G. Guagliumi, et al., the HORIZONS-AMI Trial Investigators, Bivalirudin during primary PCI in acute myocardial infarction, The New England Journal of Medicine 358 (2008) 2218–2230.

[34] L. Bonello, A. De Labriolle, P. Roy, et al., Head-to--head comparison of bivalirudin versus heparin without

glycoprotein IIb/IIIa inhibitors in patients with acute myocardial infarction undergoing primary angioplasty, Cardiovascular Revascularization Medicine 10 (2009) 156–161.
[35] G. Montalescot, U. Zeymer, J. Silvain, et al., ATOLL trial of enoxaparine in primary percutaneus coronary intervention, Lancet 378 (2011) 693–703.
[36] J.H. Chesebro, G. Knatterud, R. Roberts, Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge, Circulation 76 (1987) 142–154.
[37] The GUSTO Investigators, An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction, The New England Journal of Medicine 329 (1993) 673–682.
[38] S.V. Rao, K. O'Grady, K.S. Pieper, A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes, Journal of the American College of Cardiology 47 (2006) 809–816.
[39] R. Mehran, S.V. Rao, D.L. Bhatt, et al., Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium, Circulation 123 (2011) 2736–2747.
[40] S. Subherwal, E. D. Peterson, D. Dai, et al., Temporal trends in and factors associated with bleeding complications among patients undergoing percutaneous coronary intervention: a report from the National Cardiovascular Data CathPCI Registry, Journal of the American College of Cardiology 52 (2012) 1861–1869.
[41] S.V. Manoukian, Predictors and impact of bleeding complications in percutaneous coronary intervention, acute coronary syndromes, and ST-segment elevation myocardial infarction, The American Journal of Cardiology 104 (5 Suppl) (2009) 9C–15C.
[42] K.J. Smith, A.J. Bleyer, W.C. Little, D.C. Sane, The cardiovascular effects of erythropoietin, Cardiovascular Research 59 (2003) 538–548.
[43] M.H. Shishehbor, S. Madhwal, V. Rajagopal, et al., Impact of blood transfusion on short- and long-term mortality in patients with ST-segment elevation myocardial infarction, Journal of the American College of Cardiology. Cardiovascular Interventions 1 (2009) 46–53.
[44] R. Rossini, R. Capodanno, C. Lettieri, et al., Prevalence, predictors, and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug eluting stent, The American Journal of Cardiology 107 (2011) 186–194.
[45] S.V. Rao, I. Bernat, O.F. Bertrand, Remaining challenges and opportunities for improvement in percutaneous transradial coronary procedures, European Heart Journal 33 (2012) 251–256.
[46] S.S. Jolly, S. Amlani, M. Hamon, et al., Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials, American Heart Journal 157 (2009) 132–140.
[47] M.A. Mamas, K. Ratib, H. Routledge, et al., Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials, Heart 98 (2012) 303–311.
[48] D. Joyal, O.F. Bertrand, S. Rinfret, et al., Meta-analysis of ten trials on the effectiveness of the radial versus the femoral approach in primary percutaneous coronary intervention, American Journal of Cardiology 109 (2012) 813–818.
[49] S. Jolly, K. Niemela, D. Xavier, P. Widimský, RIVAL trial. Design and rationale of the radial versus femoral access for coronary intervention, American Heart Journal 161 (2011) 254–260.
[50] E. Romagnoli, G.B. Zoccai, A. Sciahbasi, et al., Radial Versus Femoral Randomized Investigation in ST Elevation Acute Coronary Syndrome (RIFLE STEACS), Journal of the American College of Cardiology 2012 Jul 27. Epub ahead of print.
[51] S. Subherwal, R.G. Bach, A. Y. Chen, et al., Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE Bleeding Score, Circulation 119 (2009) 1873–1882.
[52] I. Bernat, R. Rokyta, J. Koza, et al., Radiální přístup u koronárních a nekoronárních katetrizací a intervencí, Cor et Vasa 51 (4 Suppl) (2009) 59–63.
[53] D.L. Bhatt, B.L. Cryer, C.F. Contant, et al., COGENT trial, Clopidogrel with or without omeprazole in coronary artery disease. The New England Journal of Medicine 363 (2010) 1909–1917.
[54] I.J. Douglas, S.J. Evans, A.D. Hingorani, et al., Clopidogrel and interaction with pump inhibitors: comparison between cohort and within person study designs, British Medical Journal 345 (2012) e4388.
[55] W. Dewilde, O. Oirbans, F. Verheugt, WOEST trial, ESC congress, Hotline III, Munchen, August 2012.
[56] L.A. Fleischer, J.A. Beckman, K.A. Brown, et al., ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery, Journal of the American College of Cardiology 50 (2007) 159–241.
[57] M.A. Crowther, T.E. Warkentin, Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents, Blood 111 (2008) 4871–4879.
[58] P.G. Chassot , C. Marcucci, A. Delabays, et al., Perioperative antiplatelet therapy, American Family Physician 12 (2010) 1484–1489.
[59] R. Rossini, D. Capodanno, C. Lettieri, Prevalence, predictors and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug stent implantation, The American Journal of Cardiology 107 (2011) 186–194.
[60] A.O. Abualsaud, M.J. Eisenberg, Perioperative management of patients with drug-eluting stents, Journal of the American College of Cardiology. Cardiovascular Interventions 2 (2010) 131–142.
[61] J.D. Douketis, P.B. Berger, A.S. Dunn et al., The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), Chest 133 (6 Suppl) (2008) 299S–339S.
[62] M.J. Patel, S.S. Patel, N.S. Patel, N.M. Patel, Current status and future prospects of drug eluting stents for restenosis, Acta Pharmaceutica 62 (2012) 473–496.
[63] L. Mauri, D.J. Kereiakes, S. L. Normand, et al., Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug--eluting stent or bare metal stent placement for the treatment of coronary artery lesions, American Heart Journal 160 (2010) 1035–1041.
[64] M. Derogar, G. Sandblom, L. Lundell, et al., Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events, Clinical Gastroenterology and Hepatology 11 (2013) 38–42.