Haemostasis is a complex phenomenon defined as the chain of mechanisms able to maintain the integrity of a closed, high-pressure circulatory system after vascular damage. Thrombogenesis represents the main process assuring haemostasis at each level of the vascular system, and its accurate regulation guarantees the correct balance between blood flow and damage repair. An uncontrolled thrombin formation may occur in different pathological situations, finally leading to the dangerous process of thrombosis.

Atherosclerosis development and its complication into an acute coronary syndrome (ACS) recognises different pathogenetic mechanisms that involve inflammation, endothelial dysfunction, platelet activation and, finally, thrombus formation. ST-segment elevation myocardial infarction (STEMI) is paradigmatic of inappropriate thrombogenic response. In fact, complete thrombotic occlusion of epicardial coronary vessels is present in the vast majority of cases.

The currently recommended treatment of ACS is based upon early mechanical reperfusion and prompt use of potent antithrombotic drugs aimed to obtain the best chances of vessel patency restore and significant reduction of acute and late cardiovascular events. Furthermore, the widespread use of intracoronary devices, such as drug-eluting stents during percutaneous coronary intervention (PCI), also implies the necessity for prevention of potentially life-threatening device-related complications, such as early, late and very late stent thrombosis. On the other hand, the need for fast reperfusion and thrombosis inhibition must be balanced with the individual risk of bleeding for each subject, as this complication is a well-recognised cause of morbidity and mortality in post-PCI patients. With the development of more potent and rapidly acting antithrombotic agents, the choice of the right therapy for each patient should be the result of a careful consideration of the individual clinical and operative risk.

Major Mechanisms of Thrombus Formation

Thrombogenesis in ACS is often initiated by complications of vulnerable atherosclerotic plaques that are prone to rupture, mainly due to their elevated content of lipids and apoptotic cells, leading to a necro-fatty core and a thin-cap fibrous coverage. The loss of endothelial coverage seems to be also the main responsible for their thrombin-independent activation. The second pathway involves tissue factor (TF) release and its binding to factor VIIa that activates factor IX, leading to generation and, finally, platelets activation via protease-activated-receptor 1 (PAR-1) that also triggers amplification of the response by release of adenosine diphosphate (ADP), serotonin and thromboxane A2 (TXA2). In particular, TXA2 is synthesised from arachidonate by the...
cyclo-oxygenase (COX) pathway, while ADP is released by the dense granules of the platelets. Both these important mediators enhance platelets activation by autocrine and paracrine actions, interacting with G-protein coupled receptors, namely TP \( \alpha \) and TP \( \beta \) for TXA\( _2 \), and P2Y\( _1 \) and P2Y\( _12 \) for ADP. All the effectors finally trigger aggregation activating the IIb/IIIa (\( \alpha IIb/\beta 3 \)) integrin receptor for fibrinogen and vWF, but platelet activation is not uniform in the early phases of thrombus formation.\(^{10}\) Therefore, initial thrombus is a dynamic entity, with continuous platelets activation, adhesion and separation, rendering the clot architecture and shape extremely variable.

Coagulation is the other major pathway of thrombus formation, and its activation relays mainly on the release and exposure of TF, a membrane protein that is constitutively expressed by fibroblasts and smooth muscle cells, while it is inducible on monocytes and endothelial cells.\(^{11}\) Furthermore, it is known that TF is also present in circulating blood, on the surface of tiny cell-derived vesicular structures that can be captured by the P-selectin expressed by activated platelets.\(^{12}\) This form of TF is usually inactive, and can be cleaved into the active form by disulphide isomerase expressed by platelets and endothelial cells at the injury site, probably being the main enzyme responsible for fibrin deposition inside the thrombus.\(^{13}\) Once in the active form, TF forms complexes with circulating factor VIIa that are able to activate factors VII, IX and X; the binding of factor Xa to factor V promotes the production of small quantities of thrombin that probably ignites the burst of the subsequent coagulation process.\(^{14}\) In fact, the initial small amount of thrombin can activate both factors V and VII, leading to efficient conversion of prothrombin into thrombin itself by the more active complex Xa-Va. As thrombin availability is the main limiting factor for the coagulative chain burst, the final step of the conversion of fibrinogen into fibrin is greatly enhanced after the early ignition phase, and this process further propagates the thrombus, eventually leading to pathological thrombosis.

**Inhibiting Platelets Aggregation**

As previously stated, platelet activation leading to the autocrine and paracrine release of active mediators and subsequent aggregation, represents one of the two main pathways for thrombus formation. Over the years, several molecules have been discovered and used to inhibit platelet activation, but all these compounds focus on three key stages of the process: inhibition of TXA\( _2 \) formation, blockage of the P2Y\( _12 \) ADP receptor and blockage of the IIbIIIa integrin.

**Aspirin**

Acetylsalicylic acid (ASA) irreversibly blocks both COX-1 and COX-2 (more weakly) by acetylation of their active site,\(^{15}\) thus preventing prostaglandin (PGs) and thromboxane production from platelets-membrane arachidonate. In particular, COX-1 inhibition reduces prostaglandin H\( _2 \) (PGH\( _2 \)), which is a metabolic precursor of TXA\( _2 \), a potent platelet activator. Being the first synthesised effective antithrombotic agent, ASA still plays an unquestionable role in the treatment of vascular thrombosis and major cardiovascular events prevention. In classic...
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patients, independently of the treatment strategy.5,6 of 75–100 mg daily (Class:I; LOE:B). ASA is also recommended in ACS, unless contraindicated, followed by a long-term maintenance dose recommending administering an initial loading dose of 150–300 mg of Therefore, for the treatment of both non-STEMI (NSTEMI) and STEMI AMI has been then confirmed in the large ISIS-2 trial,17 showing survival benefits comparable with those achieved by streptokinase fibrinolysis. antithrombotic therapy with ASA has also been analysed and confirmed benefits comparable with those achieved by streptokinase fibrinolysis. Furthermore, ASA decreased rates of re-infarctions and non-fatal strokes at mid-term follow-up in the same study. Long-term benefits of chronic antiarrhythmic therapy with ASA has also been analysed and confirmed with dosages of 75–325 mg/day.13 In older studies, ASA proved useful for hard-endpoints prevention also in the setting of unstable angina.19 Therefore, for the treatment of both non-STEMI (NSTEMI) and STEMI patients undergoing PCI, the European Society of Cardiology (ESC) recommends administering an initial loading dose of 150–300 mg of ASA, unless contraindicated, followed by a long-term maintenance dose of 75–100 mg daily (Class I; LOE:B). ASA is also recommended in ACS patients, independently of the treatment strategy.14

Ticlopidine

The first-generation thienopyridine ticlopidine, usually administered at a dose of 250 mg twice daily, has been widely replaced by newer agents mainly due to its known adverse haematological effects (neutropenia, purpura).

Clopidogrel

The second-generation PDY12 receptor blocker drug, clopidogrel bisulphate, is a prodrug activated in the liver by a cytochrome-mediated two-step oxidation. Importantly, 85% of the administered dose is inactivated by esterase-mediated competing reactions.20 The active compound binds permanently to a free cysteine on P2Y12, inactivating it for all the platelet’s lifespan. The clinical use of clopidogrel in non-ST-elevation (NSTEMI)-ACS has been investigated in the large CURE trial, which evidenced a significant reduction in a composite of cardiovascular death, recurrent AMI or strokes when a 300 mg loading dose followed by 75 mg daily of the drug was associated to ASA in terms of ASA alone (9.3 % versus 11.4 %; p<0.001).21 In the CURRENT-OASIS 7 trial a double loading dose of 600 mg followed by 6 days of 150 mg daily of clopidogrel proved superior in preventing cardiovascular deaths/AMI and stroke (3.9 % versus 4.5 %; p=0.039), as well as stent thrombosis, in the subgroup of more than 17,000 patients undergoing PCI.22 This result is achieved at the price of more CURRENT-defined major bleedings (1.6 % versus 1.1 %; p=0.009), but without significant excess of intracranial or surgical bleedings. Due to relevant inter-individual absorption and metabolism differences, the degree of platelet inhibition is not uniform among clopidogrel-treated patients, leading to the need for more potent and reliable P2Y12 blockers.23 The current recommendations by the ESC suggest a loading dose of 300 (Class I; LOE:A) or 600 mg of clopidogrel (Class I; LOE:B) followed by a maintenance of 75 mg daily (or 150 mg until day 8) in both STEMI and NSTEMI patients when it is not possible to administer newer molecules (prasugrel, ticagrelor).24,25

Prasugrel

The third-generation thienopyridine prasugrel guarantees more rapid and predictable platelet inhibition than clopidogrel even sharing an almost identical mechanism of action based on irreversible disulphide bridging on the P2Y12 receptor.26 Unlike clopidogrel, cytochromal and uptake molecules polymorphisms do not have a great effect on the prasugrel metabolism, while an esterase-mediated intestinal reaction forms thyolactones that are then rapidly converted to the active form by the P450 cytochrome system, leading to a greater bioavailability of the active compound.27 Standard oral loading dosages of 60 mg produce peak plasmatic concentration after just 30 minutes, while 60–70 % of platelet activity is inhibited in 2–4 hours.28 In the PRINCIPLE-TIMI (“Thrombolysis In Myocardial Infarction”) 44 phase II trial, 60 mg loading dose and 10 mg maintenance dose of prasugrel achieved superior results in terms of platelet inhibition compared with a 600 mg loading dose and a 150 mg maintenance dose of clopidogrel.29 In the setting of STEMI or NSTEMI treated with PCI, the TRITON-TIMI 38 study compared a 60 mg loading dose followed by 10 mg daily maintenance of prasugrel with a 300 mg loading dose and 75 mg daily maintenance of clopidogrel, with the loading dose administered after coronary angiography.30 The trial demonstrated a significant reduction of the composite endpoint of cardiovascular death, non-fatal AMI and non-fatal stroke in the prasugrel group (9.9 % versus 12.1 %; p<0.001), with early survival advantages after only 3 days persisting at a mean follow-up of 14.5 months. Although this result was mainly driven by AMI reduction (7.3 % versus 9.5 %; p<0.001), the prasugrel-treated group also had less need for target vessel revascularisation (TVR) or definite or probable stent thrombosis. Patients with diabetes had the greatest reduction of the primary endpoint (12.2 % versus 17.0 %; p<0.001) with a relative risk (RR) reduction of 34 % compared with 13 % in the cohort without diabetes. This powerful antiplatelet action has the cost of increased major non-coronary artery bypass graft (CABG)-related TIMI bleedings (2.4 % versus 1.8 %; p=0.03) determining a net clinical harm in patients with previous stroke or transient ischaemic attack and no benefits in patients older than 75 or weighing less than 60 kg. In the overall study population the net balance between primary endpoint reduction and major non-CABG bleedings still favoured prasugrel treatment (12.2 % versus 13.9 %; p=0.004). The TRILOGY ACS trial investigated prasugrel in ACS patients not planned for PCI, failing to demonstrate reductions in a composite of cardiovascular death, non-fatal AMI and non-fatal stroke at 30 months.31 Therefore ESC recommends a 60 mg loading dose and 10 mg daily maintenance of prasugrel in P2Y12 naive patients undergoing PCI (Class I; LOE:B) after visualisation of the coronary arteries.14 Ticlopidine or clopidogrel pre-treated patients may also receive prasugrel before PCI (Class IIIa; LOE:B).2

Ticagrelor

Ticagrelor is the first representative of a new class of ADP blockers, triazolopyrimidines, which act as ADP analogues directly binding to P2Y12 causing allosteric reversible blockage of the receptor. This compound has a more powerful, rapid and predictable effect on platelet inibition than clopidogrel. Being an ADP-mimicking molecule, the drug could bind bronchial A1 receptors, possibly accounting for a unique side effect, dyspnœa, which may also be provoked by ADP accumulation and reversible P2Y12 inhibition on sensory neurons.32 Although ticagrelor is active itself, its main metabolite, produced by de-hydroxyethylation via CYP3A4, accounts for part of the effect.33 The drug peaks at 1–3 hours post loading dose, with an half-life of 6–13 hours that justifies its bi-daily administration. After 2–4 hours from an oral loading dose of 180 mg, ticagrelor inhibits platelets aggregation by 50–60 %, an effect that can be maintained with b.i.d. doses of 90 mg.34 Further increases of maintenance dosages over 90 mg produce a relatively small increment of platelet inhibition. Clinical use in intermediate to high-risk NSTE-ACS (either treated invasively or conservatively) or STEMI patients planned for primary PCI was evaluated in the PLATO trial, comparing a standard 300–600 mg loading dose and 75 mg daily maintenance dosages of clopidogrel with a 180 mg loading dose and 90 mg b.i.d. maintenance of ticagrelor.35 The ADP blocker drug was continued for 6–12 months (mean 9 months). In
the overall population, the study demonstrated a significant reduction in the composite primary endpoint of cardiovascular deaths, AMI and non-fatal strokes (9.8 % ticagrelor group versus 11.7 % clopidogrel group; p<0.001), mainly driven by a reduction of deaths (4.0 % versus 5.1 %) and AMI (5.8 % versus 6.9 %). In PLATO overall major bleedings were similar in both groups (11.6 % versus 11.2 %; p=0.43), treatment with ticagrelor was associated with significantly higher rates of non-CABG related bleedings (4.5 % versus 3.8 %; p=0.03) or spontaneous bleedings (3.1 % versus 2.3 %; p=0.01). Rare fatal intracranial bleedings were also more frequent in the ticagrelor group (0.21 % versus 0.03 %; p=0.02), as were non-procedure-related bleedings after 30 days. Like for prasugrel, the overall clinical benefit analysis in PLATO was in favour of the ticagrelor group (7.9 % versus 9.0 %; p=0.026). In CABG-treated patients, ticagrelor versus clopidogrel reduced total mortality (4.7 % versus 9.7 %; p=0.001) by decreasing both cardiovascular and non-cardiovascular deaths, while CABG-related bleedings were similar in the two treatment arms. As expected, dyspnoea was more frequent in ticagrelor-treated patients (13.8 % versus 7.8 %; p=0.001), even if this was not a significant cause of treatment discontinuation. Benign, early phase (transient) ventricular pauses were also more frequent in the ticagrelor group.

ESC guidelines recommend a ticagrelor 180 mg loading dose followed by 90 mg b.i.d. in all intermediate to high-risk ACS patients (Class I; LOE:B), regardless of the initial treatment strategy and including clopidogrel pre-treated patients, suspending clopidogrel at drug shift.""

**Cangrelor and Elinogrel**

Potential advantages of intravenous non-GPIIbIIa blockers antplatelet drugs may be appreciated in patients vomiting during the acute phase of ACS – patients unable to take oral therapy, need for rapid-onset or quick reversal of the drug effect e.g. for bridge therapy to CABG interventions. Cangrelor is a new intravenous direct-acting P2Y12 blocker characterised by almost immediate antplatelet effect, a plasmatic half-life of 3–5 minutes and rapid restoration of platelet function just 1 hour after infusion cessation.""

In the BRIDGE trial, 210 ACS or PCI patients planned for CABG were randomised to either Cangrelor or Placebo infusion after stopping ongoing P2Y12 inhibitors. Cangrelor administration until 1–6 hours before CABG did not produce an excess in surgical bleeding compared with placebo (11.8 % versus 10.4 %; p=0.76), while maintaining effective antplatelet action during the infusion.""

In the CHAMPIONS-PHONIX trial more than 11,000 patients scheduled for urgent or elective PCI were randomised to receive a 300–600 mg loading dose of clopidogrel or cangrelor infusion.""

The primary endpoint, a composite of death, AMI, ischaemia-driven revascularisation and stent thrombosis at 48 hours after PCI, was significantly reduced in the cangrelor group (4.7 % versus 5.9 %; p=0.005) with no significant differences in the rate of major bleeding. Elinogrel is another reversible direct P2Y12 blocking agent available for both oral and intravenous administration. In the phase II INNOVATE-PCI trial"" it was compared with clopidogrel in non-urgent PCI patients without relevant increase in major bleedings, but ad hoc phase III studies are still required to clarify its potential role in the clinical setting. Current ESC guidelines do not include specific recommendations for intravenous P2Y12 blockers in ACS patients undergoing PCI.""

**Dual Antiplatelet Therapy**

Although there is debate about the exact timing of administration of ADP-receptor blockers, the ESC recommends the initiation of dual antiplatelet therapy (DAPT) with ASA and a P2Y12 inhibitor (ticagrelor, prasugrel or clopidogrel) as early as possible for both STEMI and NSTEMI patients, as previously detailed (Class I; LOE:A). Unless contraindicated or discouraged by excessive risk of bleeding, DAPT should be maintained for 12 months.""

**Glycoprotein IIbIIa inhibitors**

As previously discussed, GP IIbIIa binding to several adhesive molecules, such as fibrinogen, fibronectin, vimentin and vWF, is a crucial step in aggregation and further platelet activation. Therefore, GPIIbIIa was ‘destined’ to be the target of a class of promisingly powerful antplatelet agents. The first to be developed was, indeed, a large chimeric murine/human monoclonal antibody with moderate immunogenic properties called abciximab,"" which obtained US Food and Drug Administration (FDA) approval in 1994. Two years later a lower molecular weight cyclic-peptide drug based on extracts of snake venom (disintegrin, barbourin), acting as a competitive inhibitor for fibrinogen, was introduced with the name of eptifibatide.""

The third approved GP IIbIIa inhibitor (GPI) is tirofiban, a non-peptidic small-molecule compound containing an Arg-Gly-Asp sequence that binds to the receptor inactivating it.""

Early clinical trials supported the benefits of abciximab (EPIC"" and EPILOG""), eptifibatide (IMPACT II"" and ESPRIT""), cilostazol (PLATELET-2"" and PLATELET-2 PLUS""), and tirofiban (PRISM"" and PRISM-PLUS""") for reduction of hard endpoints in urgent and elective PCI patients, at the price of an acceptable increment in bleedings. GPs have been tested either in the context of early-revascularisation strategy or conservative approach. The PURSUIT trial"" randomised 109"" NSTE intermediate to high-risk patients to receive 180 µg/kg bolus and 1.3 or 2.0 µg/kg/min maintenance dose of eptifibatide or placebo over standard therapy with unfractionated heparin (UFH) and ASA. Around 60 % of the patients underwent invasive assessment with coronary angiography while around 40 % of the patients received mechanical revascularisation either with PCI or CABG. The composite primary endpoint of death and AMI was significantly reduced in high-dose eptifibatide patients up to 30 days (8.1 % versus 10.0 %; p=0.001), with a 31 % event reduction in patients treated with early (<72 hour) PCI (11.6 % versus 16.7 %; p=0.01). Bleeding was higher in the treatment group, with a significantly higher need for blood transfusion than in the placebo group (11.6 % versus 9.2 %), with no significant differences in stroke occurrence. The GUSTO IV-ACS trial"" enrolled 7,800 NSTE patients not scheduled for PCI to either bolus plus 24 or 48 hours Abciximab infusion or placebo over standard treatment with ASA and unfractioned or low molecular weight heparin (LMWH). The study failed to demonstrate benefits of GPI in this medically treated population, showing similar rates of the composite endpoint of death or AMI at 30 days in the placebo, 24- or 48-hour abciximab infusion groups (8.0 % versus 8.2 % versus 9.1 %), and slightly increased bleeding risk. Conversely, in a meta-analysis of more than 31,000 patients with NSTEMI not routinely scheduled for early PCI, GPs performed better than placebo in reducing death or AMI at 30 days (10.8 % versus 11.8 %; p=0.015).""

Another meta-analysis of 6,458 patients with diabetes enrolled in the major GPI trials suggested potential survival benefits in this subgroup that, in contrast with the without diabetes cohort, showed a significant mortality reduction at 30 days in GPI-treated subjects (6.2 % versus 4.6 %; p=0.007).""

An important point regarding the management of GPs was to clarify whether these drugs should be initiated as early as possible prior to PCI (upstream treatment) or in the cath lab after the visualisation of the coronary tree (downstream treatment). To answer this question two major trials were conducted: ACUITY-timing"" and EARLY-ACS.""

In ACUITY-timing, 9,207 patients with NSTEMI-ACS were randomised...
to upstream or downstream strategy with any GPI, being 64 % of the overall population under thienopyridines prior to PCI. Despite non-significantly different rates of a composite of death, AMI or unplanned revascularisation at 30 days (7.9 % downstream versus 7.1 % upstream) the downstream strategy did not meet the non-inferiority goal, but major bleedings were more common in upstream-strategy patients (4.9 % versus 6.1 %; p<0.001). Similarly, in the EARLY-ACS trial, upstream use of epifibatide was not different from deferred treatment in terms of death, AMI, recurrent ischaemia or thrombotic complications during PCI (9.3 % versus 10.0 %; p=0.23). Again, early GPI use was associated with significantly higher rates of TIMI major bleedings (2.6 % versus 1.8 %; p=0.015).

As many of the older studies on GPs were conducted without the use of P2Y12 blockers, there are limited data on the usefulness of GPlibila inhibitors in addition to ASA and ADP receptor blocker drugs. In the ISAR-REACT II trial,24 2,022 patients with high-risk NSTE-ACS pre-treated with ASA and a 600 mg loading dose of clopidogrel were randomised to receive either downstream abciximab or placebo. The primary composite endpoint of death, AMI or urgent TVR at 30 days was lower in abciximab-treated patients than in the placebo group (8.9 % versus 11.9 %; p=0.03), with the benefit concentrated in the higher-risk troponine-positive subgroup. The use of GPs before primary PCI in STEMI patients, also known as ‘facilitated’ primary PCI, was not associated with a convincing improvement in outcomes, while relevant increments in bleedings were observed in the FINESSE trial.31 Furthermore, in 800 STEMI patients pre-treated with clopidogrel 600 mg enrolled in the BRAVE-3 trial, there was no significant decrease of infarct size at single-photon emission computed tomography or 30-day hard endpoints with the addition of upstream abciximab therapy.25

Overall, in ESC recommendations, usage of GPlibila inhibitors in ACS patients undergoing PCI and treated with a P2Y12 blocker, may be considered in selected populations with low bleeding risk and elevated periprocedural AMI risk (Class:I; LOE:B). Epifibatide or tiropfiban may be considered in high-risk patients undergoing PCI, pretreated with ASA alone (Class:IIa; LOE:B). Pre-treatment with tiropban or epifibatide may be considered in selected, high-risk patients in DAPT before PCI if there is evidence of ongoing ischaemia and the bleeding risk is low (Class:IIb; LOE:C). In STEMI patients, ESC guidelines recommend GPs as bailout therapy in highly thrombotic lesions or no-reflow situations (Class:IIa; LOE:C). There is modest recommendation also in patients treated with UFH and in case of patient transferral to an hub centre for primary PCI (Class:IIb; LOE:B). ESC guidelines do not currently recommend routine use of GPs upstream before invasive treatment or in ACS patients treated with DAPT not scheduled for PCI (Class:III; LOE:A).34

**Inhibiting Coagulation**

Rapid inhibition of the coagulative cascade by an injectable agent is recommended by ESC in all settings of PCI.31 Anticoagulants should be used in ACS patients undergoing PCI to reduce thrombus-related complications and minimise periprocedural thrombotic risks. Meta-analytic data suggest advantages of combination antithrombotic therapy with both antiplatelet and anticoagulant agents in ACS patients.32 Anticoagulation may be achieved indirectly or directly. Indirect anticoagulation typically requires antithrombin activation that acts as a suppressor of thrombin (UFH, LMWHs) or factor Xa (fondaparinux and partially LMWHs). Similarly, direct anticoagulation is obtained by direct inhibition of thrombin (bivalirudin, dabigatran) or factor Xa (apixaban, rivaroxaban, otamixaban).

UFH, LMWH, fondaparinux and bivalirudin are currently used in ACS (see below) and, as a general rule, switching anticoagulants in ACS patients undergoing PCI is not recommended (ESC class:III; LOE:B) except in specific cases.34

**Unfractioned Heparin**

UFH is a sulphate-polysaccharide with a mean molecular weight of 15 kDa, which is also naturally secreted by several cells such as basophils and mast cells. Almost one-third of the heparin molecules contain a pentasaccharide with high affinity for antithrombin III (AT) that binds to this molecule causing more efficient exposure of the active site, thus increasing by up to 1,000-fold the AT ability to inactivate thrombin and factor Xa.36 This anticoagulant activity may be pharmacologically reverted: in fact, protamine sulphate, originally isolated by salmon sperm, is a cationic polypeptide that forms stable ion-pair with heparin, inactivating it.37 The use of UFH for the treatment of ACS has been validated in several dated randomised trials. In the ATACS trial,40 214 ACS patients were randomised to receive either ASA 160 mg daily alone or in combination with anticoagulant therapy (i.v. UFH in the acute phase followed by a warfarin maintenance). The combination strategy significantly reduced ischaemic events (electrocardiogram [ECG] changes, MI and/or death) at 14 days (10.5 % versus 27 %; p=0.004). A meta-analysis considering six studies of NSTE-ACS patients treated with ASA plus UFH versus ASA alone found a 33 % risk reduction of death or AMI in heparin-treated patients.41 As the anticoagulant effect of UFH is quite variable between individuals, strict monitoring of the activated partial thromboplastin time (aPTT) is required to avoid lack of efficacy or haemorrhagic complications (recommended aPTT 1.5–2.5 times UNL). More recent data from the FUTURE/OASIS-8 trial suggest that in NSTE-ACS patients treated with PCI, low (50 IU/kg) versus standard (85 IU/kg) doses of UFH do not significantly reduce major peri-PCI bleeding and vascular access-site complications.42

The ESC recommends the use of i.v. bolus UFH in NSTEAMI patients proceeding to PCI (Class:I; LOE:C) at doses of 70–100 IU/Kg (or 50–60 IU/Kg in combination with GPs) to achieve aPTT 50–70 seconds and intra-procedural activated clotting times (ACT) of 250–350 seconds (or 200–250 seconds in combination with GPs).3 In STEMI patients undergoing primary PCI not pre-treated with bivalirudin or enoxaparin, Class I level C recommendation is given to UFH at the same dosages than NSTEAMI.4

**Low Molecular Weight Heparins**

LMWHs are 2–10 KDa heparin derivatives with different pharmacological effects on thrombin (more marked in greater molecular weight molecules) or factor Xa (especially lighter molecules). These drugs are well-absorbed after subcutaneous injections, bear a prolonged plasmatic half-life and bind much less than UFH to plasmatic proteins, therefore providing a more predictable anticoagulant effect.43 The most studied and clinically used molecule of this class is enoxaparin. In an A to Z trial, enoxaparin met the non-inferiority criteria in respect to UFH in NSTE-ACS patients treated with ASA and tiropiban.44 The larger SYNERGY trial30 randomised 10,027 high-risk NSTE-ACS patients to either receive UFH or enoxaparin. Again, enoxaparin proved non-inferior to UFH for a composite of death and non-fatal AMI at 30 days. However, both studies demonstrated a modest but significant increment of TIMI major bleedings in the enoxaparin group. In the randomised open-label ATOLL trial,45 enoxaparin did not reduce the primary endpoint of 30-day death, complications of MI, procedural failure and major bleeding (28 % versus 34 %; p=0.063).
but the main secondary endpoint of death, recurrent ACS, or urgent revascularisation was significantly reduced (30 % versus 52 %; p=0.015), without evidence of increase in major bleedings.

ESC guidelines recommend b.i.d. subcutaneous administration of 1 mg/kg enoxaparin for NSTEMI patients when fondaparinux is not available (Class:I; LOE:B), with no need for adjunctive anticoagulant therapy during PCI if the last dose of enoxaparin was administered less than 8 hours earlier.1 In the primary PCI for STEMI setting, the use of enoxaparin may be considered, with fewer robust evidences (Class:IIb; LOE:B).

**Fondaparinux**

Fondaparinux is a synthetic pentasaccharide similar to that contained in other glycosaminoglycans and heparin sulphates, causing reversible, indirect and selective inhibition of factor Xa by allosteric activation of AT.44 Unlike UFH, it does not affect thrombin and bears 100 % bioavailability after subcutaneous administration, long elimination half-life (17 hours) permitting one daily administration and predictable antithrombotic effects also due to low association with plasmatic proteins. Fondaparinux does not seem to induce heparin-induced thrombocytopenia (HIT), but due to its renal elimination it is contraindicated when the glomerular filtration rate is low (<20 ml/ minute). The PENTUA study42 was a dose-finding trial that randomised ACS patients to enoxaparin or fondaparinux at different daily dosages (2.5, 4, 8 or 12 mg), reporting no dose-related differences in death, MI or recurrent ischaemia after 9 days, thus suggesting the use of the lower dose. Per-protocol analysis suggested potential reduction of the endpoint in respect to enoxaparin. In the ASPIRE trial,43 350 patients undergoing elective or urgent PCI were randomised to fondaparinux 2.5 or 5 mg or to UFH. No significant differences in terms of bleeding in fondaparinux versus the UFH group were found (6.4 % versus 7.7 %; p=0.61), while a 2.5 mg dose of fondaparinux tended to have fewer bleeding events, but the study may have been undersized for adequate statistical power. The large OASIS-5 study randomised 20,078 NSTE-ACS patients to either Fondaparinux 2.5mg once daily or enoxaparin 1 mg/kg b.i.d. for an average of 5 days of enrolment.45 Fondaparinux was non-inferior to enoxaparin for a composite efficacy endpoint of death, AMI or refractory ischaemia at 9 days (5.8 % versus 5.7 %) with significantly fewer major bleedings in the fondaparinux group (2.2 % versus 4.1 %; p<0.001). Bleeding was an independent predictor for mortality and, as a consequence, hard endpoints at 6 months (death, AMI, strokes) were lower in patients treated with fondaparinux (11.3 % versus 12.5 %; p=0.007). As expected, in PCI patients treated with fondaparinux there were fewer major bleeding complications at 9 days (2.4 % versus 5.1 %; p=0.001). Although more catheter-related thrombosis were seen in the fondaparinux group, this difference disappeared with the addition of an UFH bolus at the beginning of PCI. Overall, OASIS-5 demonstrated a net clinical benefit of fondaparinux over enoxaparin in the balance of death, AMI, stroke and major bleeding (8.2 % versus 10.4 %; p=0.004). Conversely, the OASIS-6 randomised trial,46 designed to evaluate fondaparinux in the setting of STEMI, was not able to provide definitive results and raised multiple criticisms, mainly due to the heterogeneity in the medical and invasive treatment of the enrolled patients. Particularly, even if the authors concluded for mortality and reinfarction reduction at 30 days in the fondaparinux group, no benefits were observed in the PCI population with significantly higher guiding catheter thrombosis and other coronary complications (abrupt closure, no-reflow, dissection, new thrombus formation).

ESC recommendations for fondaparinux are therefore strong in NSTEMI patients and administration of a daily dose of 2.5 mg subcutaneously seems associated with the most favourable efficacy–safety profile among other anticoagulants (Class:I; LOE:A). In case of fondaparinux pre-treatment, in order to lower the risk of intraprocedural thrombosis, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GP Iib/IIa receptor inhibitors) should be added at the time of PCI (Class:I; LOE:B).1 Conversely, fondaparinux is not recommended in patients with STEMI undergoing PCI (Class:II; LOE:B).4

**Bivalirudin**

Bivalirudin is a synthetic peptide congener of the natural compound hirudine, found in the saliva of the medicinal leech Hirudo medicinalis. The drug acts as a potent, rapid and reversible inhibitor specific for thrombin that binds both to the catalytic site and to the substrate-recognition site of circulating and clot-bound thrombin, inactivating it. Thrombin itself has the ability to slowly cleave the bond with bivalirudin, restoring its procoagulant properties. The molecule does not bind to plasmatic proteins, therefore producing predictable anticoagulant effects that may also be monitored with routine coagulative tests (APTT, ACT).21 Furthermore, bivalirudin does not seem to induce HIT. The increasing awareness of the detrimental effects of bleeding on outcome of ACS patients represents the premise to appreciate these characteristics of bivalirudine, especially in invasively treated subjects. In the REPLACE-2 trial21 bivalirudine (0.75 mg/kg followed by 1.75 mg/kg/ hour during the intervention) plus provisional GPI was compared with UFH plus planned GPI over DAPT in 6,010 patients undergoing elective or urgent PCI (45 % of the patients had unstable angina). Non-significant differences were seen in the primary composite 30-day endpoint of death, MI, urgent repeated revascularisation or in-hospital major bleeding (9.2 % bivalirudine versus 10.0 % UFH). However, bivalirudine treatment reduced both in-hospital major bleeding (2.4 % versus 4.1 %; p<0.001) and minor bleeding (13.4 % versus 25.7 %; p<0.001). In the setting of ACS, the ACUTY trial22 randomised 13,819 patients planned for invasive strategy to one of three anticoagulant regimens: unfractionated heparin or enoxaparin plus a GP Iib/IIa inhibitor; bivalirudin plus a GP Iib/IIa inhibitor or bivalirudin alone. Bivalirudin was started with an i.v. bolus of 0.1 mg/kg and subsequent infusion of 0.25 mg/kg/h, followed by an additional bolus of 0.5 mg/kg and infusion of 1.75 mg/kg/h, stopping infusion after PCI. The composite main endpoint of death, MI or unplanned revascularisation for ischaemia at 30 days was not different between bivalirudine/GPI and heparin/GPI (7.7 % versus 7.3 %), as was major bleeding (5.3 % versus 5.7 %) or net clinical benefit. The therapy with bivalirudine alone proved non-inferior to heparin/GPI in terms of the composite main endpoint (7.8 % versus 7.3 %), while significantly reducing major bleeding (3.0 % versus 5.7 %; p<0.001) and improving the net clinical outcome (10.1 % versus 11.7 %; p=0.02; RR=0.86). The rate of major bleeding was mildly raised in patients with <60 ml/minute creatinine clearance, but similar for all anticoagulant regimens. One sub-study of ACUTY investigated the therapy switch from UFH/LMWH to Bivalirudin at the time of PCI, reporting similar incidence of ischaemic events (6.9 % versus 7.4 %, p=0.52), less major bleeding (2.8 % versus 5.8 %; p<0.01) and improved net clinical outcomes (9.2 % versus 11.9 %; p<0.01), thus suggesting that shifting to Bivalirudin may be favorable to improve prognosis.21 In the setting of STEMI, the HORIZON-AMI trial randomised 3,602 primary-PCI patients presenting within 12 hours of symptoms onset to receive either UFH/GPI or bivalirudine alone. Major bleeding was substantially reduced with bivalirudin (4.9 % versus 8.3 %; p<0.001), as were 30-day rates of cardiac (1.8 % versus 2.9 %; p=0.03) and all-cause death (2.1 % versus 3.1 %; p=0.047). Although the authors...
reported an increment of acute stent thrombosis with bivalirudine alone, this difference disappeared at 30-day analysis. Possible advantages of early therapy with bivalirudin over UFH plus optional GPIs, administered during the transportation to a HUB centre for primary PCI, were investigated in the EUROMAX randomised open-label trial\(^5\) enrolling 2,218 patients with STEMI presenting within 12 hours. This study confirmed the reduction in major bleedings in the bivalirudin arm, driving the composite primary endpoint (death and major non-CABG related bleedings at 30 days) towards significance (5.1 % versus 8.5 %; RR 0.60; p<0.001), despite the persisting increment in acute stent thrombosis (1.1 % versus 0.2 %; p=0.007). Conflicting evidence arise from the single-centre HEAT PPCI study recently presented at the 2014 American College of Cardiology congress, which randomised 1,829 patients with STEMI receiving primary angioplasty in Liverpool between 2012 and 2013 and bivalirudin or UFH before the procedure. The primary endpoint, a composite of all-cause mortality, stroke, reinfarction and target lesion revascularisation (TLR), was higher in the bivalirudin group (8.7 % versus 5.7 %; p=0.01), with more stent thrombosis (3.4 % versus 0.9 %; p=0.001), but no difference in terms of major or minor bleedings between the two strategies. Concerns were raised about the value of these monocentric data in comparison with the discussed larger multicentric trials that may deserve more credit, but the topic is object of current interest and debate.

To date, ESC guidelines for NSTEMI recommend Bivalirudin with bailout GPIs over UFH plus GPIs (Class I; LOE B). In NSTEMI patients, bivalirudin is recommended as an alternative to UFH plus GPIs in subjects undergoing early PCI especially if at high bleeding risk (Class I; LOE B).

Novel Anticoagulant Agents

Lowering thrombotic complications of ACS and modulating the effects of thrombin on both coagulative cascade and platelets aggregation represent the rationale for potential use of oral anticoagulants in the therapy of ACS-patients. In fact, several studies and meta-analyses have been conducted in the past to test the efficacy of warfarin for the improvement of clinical outcomes of these patients.\(^6\)\(^7\) However, although these studies almost consistently found significant reductions in death, AMI or ischaemic stroke, major bleedings were markedly increased by two to threefold in warfarin-treated subjects, or even when DAPT was started.\(^8\) The relatively high incidence of cardiovascular death and AMI at 5 years after an ACS, which is approximately 25 to 30 % even in the DAPT era, pushes the research towards trying novel oral anticoagulants (NOA) in secondary prevention of ischaemic events.\(^9\) Factor Xa direct inhibitors rivaroxaban and apixaban have been challenged in ACS phase III trials, but produced inconsistent effects on hard endpoints while clearly raising the risk of major bleeding. The apixaban phase III APPRAISE-2 trial was prematurely stopped due to excess of bleeding in the treatment group. In the ATLAS ACS-2 trial, 2.5/5 mg of Rivaroxaban twice daily combined with ASA or ASA plus clopidogrel demonstrated a statistically significant reduction of death from cardiovascular causes, MI or stroke compared with placebo at 13.1 months. The authors also described a reduction in all-cause and cardiovascular mortality with an increase in the risk of major bleeding and intracranial haemorrhage, but no increase in the risk of fatal bleeding.\(^10\) The direct thrombin inhibitor dabigatran was also tested in the unpublished RE-DEEM phase II trial, but no further development of its ACS-indication are planned by the producing industry. Another phase III study on the i.v. factor Xa inhibitor olatixaban is currently ongoing.

Therefore, despite the consistent physiological rationale, the use of NOA is not routinely recommended in ACS patients by current ESC guidelines and deserves more in-depth evaluation.

Conclusions

The outcome of NSTEMI and STEMI patients undergoing PCI is a delicate balance between the disease’s natural history, medical therapy, early invasive treatment and the potential risk of harm of specific interventions, especially major bleeding. In order to reduce thrombotic complications, powerful and specific drugs to inhibit both platelet aggregation and the coagulative cascade have been developed, with the patient-tailored combination being an important key to therapeutic success. In this era of DAPT and direct anticoagulant agents, ACS are still associated to relevant adverse long-term outcomes. Better patients selection and ischaemic/bleeding risk classification other than future progresses in pharmacological research are urgently needed to reduce this persistent gap between therapeutic options and actual long-term event-free survival.