Review Article

Parenteral Anticoagulants in Acute Coronary Syndromes and Interventional Cardiology: A Consensus Document

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Parenteral anticoagulants constitute an important component in the therapy of acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI), exerting their action either indirectly by potentiating antithrombin (AT), an endogenous inhibitor of various activated clotting factors, or by direct inhibition of an activated clotting factor (Figure 1).[1-3] Unfractionated heparin (UFH), low molecular weight heparins (LMWH: anti-IIa and anti-Xa agents) and the pentasaccharide fondaparinux, as well as danaparoid (anti-Xa agents) have indirect-acting anticoagulation properties. Direct-acting inhibitors, such as the anti-thrombin (i.e. anti-IIa) agents bivalirudin, lepirudin, desirudin and argatroban, act independently of the presence of AT (Table 1).[4]

Peri-procedural anticoagulation has been an important adjunctive treatment in interventional cardiology. Patients with an ACS, whether without elevation of the ST segment in the electrocardiogram (NSTEACS) or with ST-segment elevation myocardial infarction (STEMI), routinely receive parenteral anticoagulation in the coronary care unit. After thrombolysis in STEMI patients, parenteral anticoagulation is also administered. The treatment of increasingly complex coronary artery disease with PCI dictated a more aggressive antithrombotic therapy, including more potent adenosine diphosphate receptor antagonists and provisional intravenous (IV) antiplatelet agents, such as the platelet glycoprotein IIb/IIIa receptor inhibitors (GPI). Whereas such antithrombotic regimens improve treatment efficacy, they also increase the bleeding risk. Interventional cardiologists have been more concerned about ischaemic complications rather than severe haemorrhagic episodes, considering the latter as an isolated, correctable event. Nonetheless, major in-hospital haemorrhages after an ACS are associated with poorer prognosis compared with patients who do not sustain such an episode.[5] Beyond the recognised baseline risk factors, invasive procedures and drug overdosing are frequent situations associated with increased bleeding risk and in-hospital death. This may be the case in an older woman who has been unsuccessful-

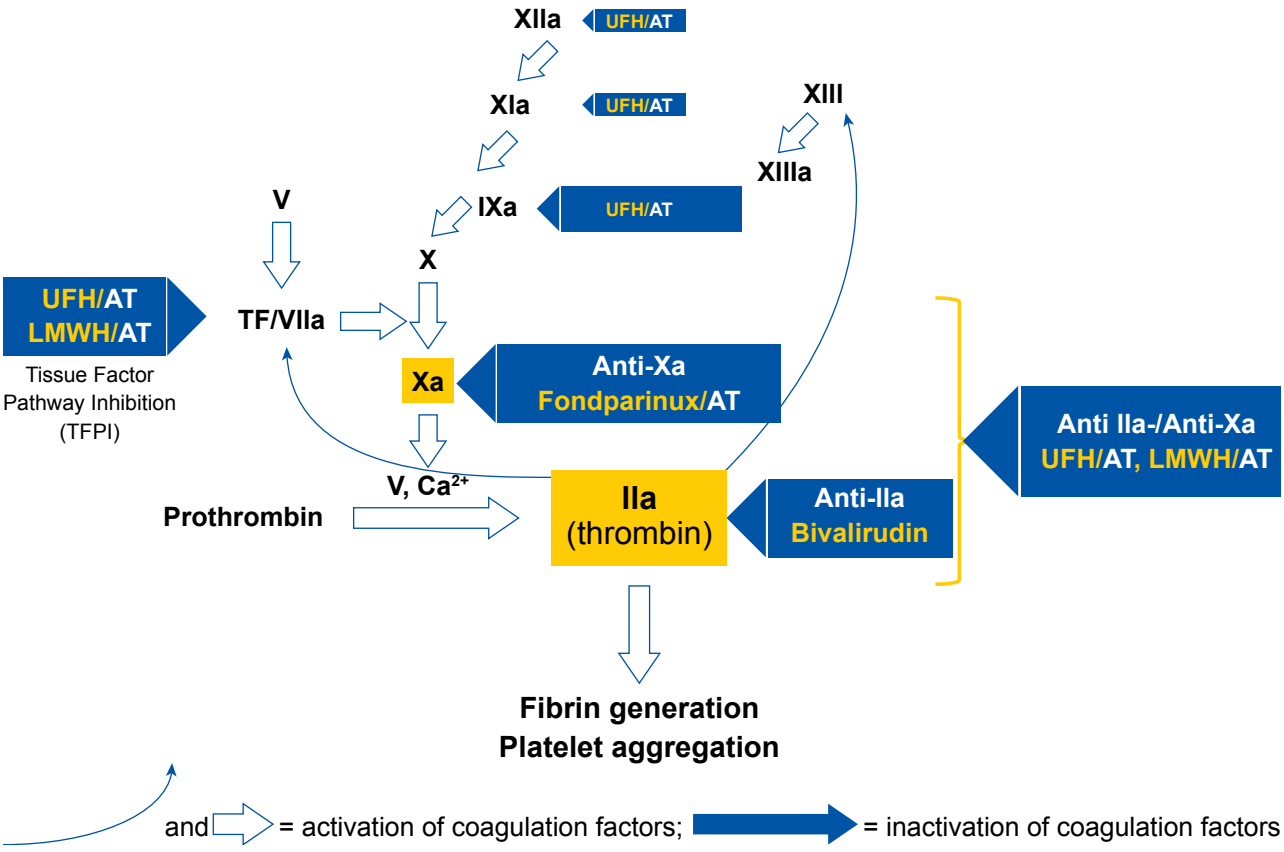

Figure 1. Inactivation of coagulation factors by the anticoagulant drugs. Parenteral anti-IIa anticoagulants act either indirectly, i.e. requiring AT (UFH, enoxaparin), or directly, i.e. not requiring AT (bivalirudin, as well as hirudin and argatroban). The parenteral anti-Xa anticoagulants fondaparinux and danaparoid act indirectly, by potentiating the antithrombin action. The UFH/AT complex inactivates less sensitively the factors XIIa, XIa and IXa (in small blue arrows) over IIa and Xa (see text for details). AT – antithrombin; UFH – unfractionated heparin. LMWH – low molecular weight heparin.

ly thrombolysed for STEMI, received dual antiplatelet therapy (DAPT) and enoxaparin, and underwent transfemoral instead of transradial rescue PCI. In contrast to UFH, the other parenteral anticoagulants are partially or totally excreted through the kidney, thereby requiring dose adjustments. Other dose modifications may be necessary according to age, body weight or additional antiplatelet use, classically UFH with a GPI in patients undergoing PCI.

Unfractionated heparin

Pharmacology

UFH is a heterogeneous group of glycosaminoglycans made in mast cells and purified from bovine or porcine sources, though information regarding its complete chemical structure is still elusive. UFH consists of muco-polysaccharide and poly-sulphated molecules with a molecular weight of 3-30 kDa (on average 11-17 kD), corresponding to an average of 45 saccharides). UFH indirectly inhibits coagulation factors IIa and Xa, through interaction with AT. A $\geq$18-saccharide sequence is essential for the anti-IIa activity, whereas a high-affinity 5-saccharide sequence (found in one third of UFH molecules) is necessary for both the anti-IIa and anti-Xa activity of UFH.[1-3] The AT action of UFH encompasses lower thrombin production and neutralisation of plasma thrombin, thus resulting in inhibition of thrombin-induced activation of platelets and coagulation factors. The bioavailability of UFH is better if it is administered IV rather than subcutaneously (SC). The non-specific binding of UFH to plasma proteins renders its anticoagulant activity not completely predictable. Furthermore, UFH does not inhibit clot-bound thrombin, whereas platelet factor (PF)-4 influences its anticoagulant effects. The plasma clearance of therapeutic doses of the drug is achieved via a rapid cellular binding (macrophages,

endothelial cells) and a slow renal excretion. No dose adjustment is needed according to plasma creatinine clearance.[1-3] Abrupt cessation of UFH infusion has been associated with rebound activation of the coagulation cascade and increased plasma thrombin activity. Aspirin suppresses only partially, if at all, this rebound effect, but DAPT may be more effective. Therefore a gradual discontinuation of the UFH infusion should be recommended.

Adverse reactions

Haemorrhagic complications

Bleeding episodes have a rough association with anticoagulation levels of UFH, thereby necessitating monitoring of anticoagulation for an optimal antithrombotic effect. For this purpose, the activated partial thromboplastin time (aPTT) is commonly used. The aPTT remains the most frequently used method for anticoagulant monitoring. The aPTT should be measured ~6 hours after the bolus dose of heparin and the infusion dose adjusted according to the daily results with the aid of nomograms.[6] aPTT intensity should be titrated to a heparin level equivalent up to 0.6 U/mL for ACS or an anti-factor Xa level of 0.30 to 0.7 U/mL. The goal is to achieve an aPTT of 60-85 s. In the aPTT ranges of 50-70 s, the frequency of death, myocardial infarction (MI) or stroke in observational studies was found to be lowest. Furthermore, a patient/control aPTT ratio of 1.5-2.5 (using various reagents) has been found to protect against thrombotic complications.[1-3]

The activated clotting time (ACT) serves for the bedside monitoring of heparin therapy during invasive cardiovascular procedures. The ACT is a whole blood test that makes use of the stimulation of the intrinsic coagulation pathway with particulate agonists such as kaolin (Hemotec®) or celite (Hemochron®). The two ACT tests are not interchangeable.[7] The anticoagulation level in the extreme UFH range is better reflected by ACT rather than aPTT values. Ischaemic end-points in patients undergoing PCI with stent placement have been found to remain stable with ACT values to as low as 200 s and bleeding events to increase with higher ACT levels, especially with GPI treatment.[1-3]

In patients who sustain a severe haemorrhage, protamine sulphate should be used as an antidote. Protamine is an arginine-rich, cationic peptide that binds to either UFH or LMWH and forms a stable ion pair, which does not have anticoagulant activity. Protamine sulphate neutralizes 90% of the anti-IIa activity and 100% of the anti-Xa activity of UFH, and may be administered slowly IV (1 mg/100 U of UFH if given in the preceding 4 hours). Allergic reactions, especially in individuals with fish allergy or on therapy with insulin (Protaphan), are not uncommon and may be lethal.[1-3]

Osteopenia

The binding of UFH with osteoblasts results in activation of osteoclasts and osteoporosis. It is unknown whether this side effect persists or not after drug discontinuation.

Thrombocytopenia

Thrombocytopenia appears either early, mild and transiently in 10-20% of patients as a result of direct UFH-platelet interaction, or later, between the 5th and 10th day, in 1-5% of patients, as a result of immune-mediated platelet activation (heparin-induced thrombocytopenia [HIT]). In HIT, IgG antibodies are directed against a heparin–PF-4 complex by binding platelets through the Fc receptor.[8-10] This leads to platelet activation and the formation of microparticles as well as platelet-rich thrombi at sites of pre-existing pathology, along with a drop in platelet count to between 30,000 and 50,000 /μL. HIT can be induced by small amounts of heparin in flush and appears within hours as an anamnestic response, or rarely after the 15th day of UFH exposure. Thromboembolic sequelae are evident in 25-50% of HIT cases and include pulmonary embolism, ischaemic limb necrosis necessitating limb amputation, acute MI and stroke. Prompt recognition and drug replacement are therefore of paramount importance.[8-10] The final diagnosis is facilitated by clinical scoring systems and commercially available immunoassays, both of which have high sensitivity and negative predictive value, but low or modest specificity and positive predictive value. The 4Ts score assesses the magnitude of **T**hrombocytopenia, the **T**iming of thrombocytopenia, the presence of **T**hrombosis, and no o**T**her explanation for thrombocytopenia.[10] In confirmed HIT, the patient is anticoagulated on an alternative therapy.

Clinical use of UFH

Acute coronary syndromes

Following disruption of a vulnerable plaque, tissue factor (TF) is released and forms complexes with ac-

tivated factor VII (VIIa). This TF:VIIa complex leads to conversion of factor X to its active form (Xa). A single molecule of factor Xa is capable of downstream production of several thrombin molecules. Thrombin degrades plasma fibrinogen and generates fibrin, and simultaneously it potently activates platelets via binding to the platelet protease activated receptor-1 (PAR-1), leading to the formation of platelet aggregates by cross-bridging of ligands such as fibrinogen to the platelet GPIIb/IIIa receptors.[11]

Unstable angina

Unfractionated heparin emerged as an important mainstay treatment in addition to aspirin, and dose optimization according to body weight has been developed (see recommendations).[12] In meta-analyses, UFH, alone or in combination with LMWH, in comparison with non-heparin administration was shown to reduce death or MI rates. The benefit of heparin in NSTEACS disappeared in the mid-term, probably because of rebound thrombin generation after the cessation of UFH therapy. The duration of UFH therapy varied across studies; therefore, it is not known how long UFH should be continued.[13,14]

Thrombolysis for STEMI

There is still controversy as to whether UFH should be used in thrombolysed STEMI.[15] Non-specific thrombolytic agents result in a systemic coagulopathy, fibrinogenopenia and massive production of fibrinogen/fibrin degradation products, and are therefore themselves considered as anticoagulants. Although the use of adjunct UFH is not straightforward, streptokinase-enhanced thrombin activity has been argued as the rationale for anticoagulant treatment after thrombolysis with non-specific agents. The indication for anticoagulation appears more clear for the fibrin-specific agents, as they induce a smaller systemic coagulation effect with little depletion of coagulation factors. Nevertheless, an increase in thrombin activity is also seen. The duration of UFH after thrombolysis may extend to ≥48 hours, but definite supportive data are lacking.[15]

A high SC dose of UFH as compared with placebo in thrombolysis with streptokinase did not affect ischaemic outcomes but increased major bleeding rates in two mega-trials.[16,17] In a meta-analysis, mostly with non-specific agents, UFH over placebo in addition to aspirin for 2-4 days would prevent 5 deaths and 3 reinfarctions per 1000 patients treated in-hospital with a trade-off of 3 more major bleedings.[18] In the streptokinase arm of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-1 trial, mortality was similar whether UFH was administered SC or IV, but reinfarction rates, as well a trend for more severe haemorrhagic events and strokes, favoured the SC route.[19] These data reveal the absence of any benefit of SC UFH in comparison with placebo and the disadvantage of IV over high-dose SC UFH.

Fibrin-specific agents demonstrate less anticoagulant activity in comparison with the non-specific agents. Intravenous UFH over placebo improves infarct-related artery patency rates[20] and slightly decreases death/MI, while increasing rates of major bleeding and stroke.[15,18] However, given the 14% mortality reduction conferred by the combination of alteplase plus IV UFH over streptokinase plus UFH in the GUSTO-1 trial,[19] a heparin regimen has been adopted in thrombolytic therapy.

The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction (ExTRACT-TIMI)-25 Study compared UFH with enoxaparin and showed a higher incidence of death or MI at 30 days, largely as a result of an almost 50% increase in incident reinfarction but lower rates of major bleeding in the UFH group.[21] In the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 trial, tenecteplase + weight-adjusted UFH was tested vs. tenecteplase + enoxaparin vs. half-dose tenecteplase + abciximab + UFH.[22] The lower UFH dose in the ASSENT-3 compared with the fixed UFH dose in the ASSENT-2 trial resulted in fewer bleeding events without compromising incident ischaemic complications.

Non-primary PCI

Thrombus formation is a common finding at the angioplasty site, whether with balloon only or with stent deployment, and UFH has been used as a *sine qua non* since the beginning of the coronary angioplasty era. Angioplasty without stents, i.e. plain old balloon angioplasty (POBA), was associated with acute vessel closure in almost 12% of patients, and higher ACT values were linked with the lowest incidence of ischaemic complications ACT.[23] Abciximab use demonstrated a low frequency of ischaemic complications and acceptable haemorrhagic event rates over an ACT range between 200-300 s, while ACT >400 s in-

creased ischaemic risk, possibly as a result of dose-dependent platelet activation.[23] In the stent and DAPT era, ACT appears not to correlate with ischaemic complications, whereas higher ACT values are associated with bleeding complications.[24] Consequently, the use of ACT monitoring is decreasing. Lower UFH allows for earlier sheath removal and discharge to a step-down unit, and on a background of abciximab treatment reduces bleedings without compromising efficacy.[25]

Unfractionated heparin has been tested in comparison with newer anticoagulants and in different dosages in NSTEACS. The results of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial will be discussed below. A German trial compared high-dose (140 U/kg) UFH with bivalirudin in clopidogrel pre-treated patients with unstable angina. UFH was comparable to bivalirudin in terms of efficacy, but was associated with a higher incidence of major bleeding.[26] Focusing on high-risk NSTEACS patients with an intended invasive strategy, the Superior Yield of the New Strategy of Enoxaparin, Revascularization and GPI (SYNERGY) trial showed that the 2 anticoagulants were similar with respect to death or nonfatal reinfarction at 30 days, but major bleedings were lower in the UFH group.[27] The Fondaparinux with Unfractionated heparin dUring Revascularization in Acute coronary syndromes/Organization for the Assessment of Strategies for Ischemic Syndromes (FUTURA/OASIS)-8 trial compared IV low-dose UFH (50 U/kg), or ACT-adjusted, standard-dose UFH (85 U/kg without and 60 U/kg with GPI), among NSTEACS patients initially treated with fondaparinux undergoing PCI.[28] The composite primary end-point of any bleeding and major vascular access-site complications $\geq$48 hours was similar between the 2 study groups (odds ratio [OR] 0.80, 95% confidence interval [CI]: 0.54-1.19; p=0.27). The rates of major bleeding were not different, but the rates of minor bleeding were lower in the low-dose UFH group. Ischaemic complications were marginally higher in the low-dose group (OR 1.58, 95% CI: 0.98-2.53; p=0.06).[28]

Primary PCI

In STEMI, a variable amount of thrombus exists in the culprit lesion of the infarct-related artery, platelet hyperactivity occurs, and antiplatelet agents exert a delayed antithrombotic effect. For ethical reasons, no randomised comparison of UFH with placebo has been performed in this setting. The duration of therapy with UFH is usually confined to the peri-procedural time, unless specific indications dictate prolonged use (e.g. complicated POBA, large coronary thrombus, extensive MI, left ventricular apical thrombus, atrial fibrillation or mechanical valves). In primary PCI, ACT may be used for guiding anticoagulation but should not cause treatment delay. Newer anticoagulants have been tested over UFH in primary PCI. In the OASIS-6 trial, fondaparinux was compared with either placebo or UFH in STEMI patients. Patients receiving UFH for primary PCI experienced a trend toward fewer events as compared with the fondaparinux patients in the first 2 days, whereas the frequency of bleeding was similar in the 2 groups.[29] In the Acute Myocardial Infarction Treated with primary angioplasty and intravenous enoxaparin Or unfractionated heparin to Lower ischemic and bleeding events at short- and Long-term follow-up (ATOLL) trial, UFH was compared with IV enoxaparin. The two anticoagulants showed similar rates of the primary end-point of death, complications of MI, procedure failure, or major bleeding, as well as of major haemorrhage alone.[30] The UFH over bivalirudin comparison is discussed later.

Transradial coronary procedures

The use of the transradial rather than the transfemoral route for coronary angiographies and PCIs is associated with lower access site haemorrhagic complications. Parenteral anticoagulants are administered peri-procedurally to minimise the risk of radial artery occlusion (RAO) and as adjunctive PCI pharmacotherapy. There are no convincing data on the optimal UFH dose necessary to reduce RAO rates. At present, a 5000 U UFH dose given IV appears mandatory but, higher doses, up to 85 or even 100 U/kg bolus, may be a better option for this purpose. In PCI, the transradial access allows the administration of the highest recommended UFH dose, without fear of a clinically relevant excess of entry site bleedings.[31]

Transcatheter aortic valve implantation (TAVI)

Patients undergoing TAVI are very old, frail, high-risk individuals who are prone to experiencing major complications during the procedure, including severe bleeding or vascular trauma. The large TAVI devices may cause arterial damage and haemorrhage even after meticulous use. Unfractionated heparin is given during TAVI, usually after insertion of the regular sheath and prior to insertion of the large sheath. A target ACT of $\geq$ 300 s is

Table 1. Comparative properties of unfractionated heparin, enoxaparin, fondaparinux, and bivalirudin.

	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Factor Xa:IIa inhibition	1:1	3-4:1	100% Xa	100% IIa
Antithrombin dependency	Yes	Yes	Yes	No
Non-specific binding	Yes	Partial	No	No
PK/PD variability	++	+	-	-
Anticoagulation monitoring	Yes	No	No	No
Inhibits fibrin-bound thrombin	No	No	No	Yes
Activates or aggregates platelets	Yes	Less	Less	Inhibits
Half-life	Variable with dose, about 60 min IV	300 min SC; 90-120 min IV (0.5 mg/kg)	17 h SC	25 min IV
Chronic kidney disease	Non-renal excretion (no dose adjustment)	Renal excretion (dose adjustment)	Renal excretion (dose adjustment)	Renal excretion (dose adjustment)
Risk of HIT	Yes	Lower	Low	No
Osteoblasts (osteopenia)	Yes	Reduced	No	No
Special antidote	Yes	Less effective	No	No

UFH – unfractionated heparin; PK/PD – pharmacokinetic and pharmacodynamic; HIT – heparin-induced thrombocytopenia; SC – subcutaneous; IV – intravenous.

recommended throughout the procedure. Anticoagulation reversal with protamine sulphate can be undertaken but is not necessary when the bleeding risk is low.[32]

Low molecular weight heparins

Pharmacology

LMWH are polysulphated glycosaminoglycans derived from UFH by chemical or enzymatic depolymerisation. The molecular weight of LMWH is on average 4-5 kDa (range 2-9 kDa), corresponding to 1/3 of the molecular weight of UFH or to 15 pentasaccharide units. LMWH demonstrate increased inhibitory activity against factor Xa over thrombin, with an anti-Xa to anti-IIa ratio ranging from 2:1 to 4:1, and better pharmacokinetic properties than UFH. The anti-Xa activity of LMWH is mediated by the interaction of a unique pentasaccharide sequence (found in <1/3 of LMWH molecules) with AT.[2,3] Because of the different depolymerisation methods, LMWH are somewhat different compounds and are therefore not interchangeable on a unit-to-unit basis. The lower protein and cell binding of LMWH explain the better dose-response relationship and the longer plasma half-time, respectively, in comparison with UFH. As compared to UFH, the reduced binding of LMWH to platelets/PF-4 is associated with a lower risk of HIT and the reduced bindings with osteoblasts with less osteopenia. (Table 1).[2,3] The bioavailability of LMWH is ~90%, the elimination half-time 3-6 hours, and the peak anti-Xa activity 3-5 hours after SC injection. Since LMWH are excreted from the kidney, chronic kidney disease may dictate dose adjustment or may even be a contraindication for drug use. Among LMWH, enoxaparin is the most studied compound. When creatinine clearance is <30 mL/min, half of the usual therapeutic dose or anti-Xa monitoring or alternative therapy with UFH is advised. Prophylactic doses of enoxaparin in renal insufficiency do not result in excessive plasma accumulation of the drug.[2,3] Monitoring of therapy according to anti-Xa levels is usually not required, with the exception of pregnant women, obese patients and those with renal insufficiency.

Adverse reactions

These include haemorrhagic complications, which are more likely in the presence of chronic kidney disease, as well as osteopenia and thrombocytopenia, which are less frequent than with UFH.[2,3] In the case of severe bleeding, anticoagulation with LMWH can be partially reversed by administering protamine sulphate. This antidote neutralises the anti-IIa, but only partially and variably the anti-Xa effects of LMWH. In enoxaparin-induced bleeding within 8 hours after its administration, protamine sulphate can be given in a dose of 1 mg/1 mg enoxaparin (i.e. per 100 anti-Xa enoxaparin units). If bleeding persists after the first dose, additional low-

er doses may be administered.[2,3] As excess bleeding was encountered in enoxaparin patients undergoing PCI with anticoagulant switching, this approach should be avoided.[26]

Clinical use of LMWH

Acute coronary syndromes

NSTEACS

Michalis et al found lower rates of ischaemic complications at 7 days favouring enoxaparin as compared with tinzaparin, whereas bleeding rates were similar between the 2 patient groups.[33] In 2 unstable angina trials, enoxaparin was associated with a pooled 20% reduction in death and serious cardiac ischaemic events, without any increase in major haemorrhages.[34] Dalteparin, nadroparin or enoxaparin had similar efficacy in comparison with UFH, but haemorrhages were fewer in the enoxaparin group.[35-37] Furthermore, patients receiving enoxaparin over UFH were less likely to experience ischaemia, as detected by continuous ECG evaluation, death or MI, and major, non-coronary artery bypass surgery (CABG)-related major bleedings.[38] In a meta-analysis, enoxaparin was not found to reduce mortality, but was more effective than UFH in preventing death or MI, with a similar incidence of major bleedings,[39] an advantage that appeared to become neutral when an intended invasive strategy had been planned.[27]

Extended LMWH therapy over placebo

With one exception, no benefit regarding ischemic events combined with an invariably increased rate of haemorrhages was shown in the LMWH groups.[36,40,41]

STEMI and thrombolysis

In the ASSENT-3 trial, the relative risk (RR) for 30-day ischaemic complications in the full-dose tenecteplase + enoxaparin vs. full-dose tenecteplase + weight-adjusted UFH was 0.74 (95% CI: 0.63-0.87; p=0.0002).[22] In the setting of pre-hospital thrombolysis in the ASSENT-3 PLUS trial, enoxaparin reduced in-hospital reinfarction and refractory ischaemia, but increased total stroke and intracranial haemorrhages. In a pooled analysis of the two trials, the efficacy and the combined end-point of efficacy plus safety was favourable for enoxaparin.[42] Women aged >75 years on enoxaparin vs. UFH patients carried a 10-fold higher risk of stroke.[42] Therefore, in the ExTRACT-TIMI 25 Study a specific enoxaparin dosing regimen was implemented.[21] In a meta-analysis, LMWH over placebo reduced both mortality and reinfarctions when given for 4-8 days after thrombolysis with non-specific agents, with a trade-off of increased absolute rates of major bleeding and intracranial haemorrhage by 0.7% and 0.3%, respectively. An updated meta-analysis including the ExTRACT-TIMI 25 study confirmed the reduction in reinfarctions and the increase in major bleedings over UFH.[18,43]

Meta-analysis of enoxaparin in comparison with UFH on primary or secondary PCI and PCI outside the STEMI settings

A meta-analytic clear advantage of enoxaparin for primary and a marginal benefit for secondary PCI after STEMI has recently been reported. In stable and NSTEACS patients, mortality and major bleeding rates were similar between the 2 heparins.[44]

Fondaparinux

Pharmacology

Fondaparinux (Arixtra®) is a synthetic pentasaccharide of heparins, which binds AT with increased affinity. Fondaparinux has a molecular weight of 1.7 kDa, a half-time of 17-21 hours, and specific anti-Xa activity of 700 units/mg, which is 7-fold higher than that of LMWH.[3] Fondaparinux binds to and enhances the AT reactivity with factor Xa, thus leading to the formation of an AT-Xa covalent complex. Fondaparinux is then released from AT and is available to activate additional AT molecules. Since fondaparinux is a short-chain molecule, it cannot bridge AT to thrombin and therefore lacks any anti-thrombin activity. Treatment with fondaparinux is associated with a very low risk of HIT, while antigenic reactions are virtually absent. Based on i) the almost complete bioavailability after SC fondaparinux injection, ii) the lack of variability in the anticoagulant response, and iii) its long half-life, fondaparinux can be administered to NSTEACS patients in a fixed daily dose of 2.5 mg SC, without the need of coagulation monitoring.[3] Fondaparinux is nearly completely excreted from the kidneys; consequently, its use is contraindicated in

patients with creatinine clearance of <30 mL/min. Fondaparinux does not bind and cannot be neutralised by protamine, the antidote for heparin. Thus in uncontrollable bleeding, recombinant factor VIIa may be effective. [3]

Clinical use of fondaparinux

Fondaparinux was evaluated in dose-finding phase II studies in elective PCI, NSTEACS and STEMI. The drug appeared at least as safe and efficacious as heparins, without a dose-response relationship.[3]

NSTEACS

The OASIS-5 trial compared fondaparinux with enoxaparin in high-risk NSTEACS patients, who were followed for a minimum of 90 days and a maximum of 180 days. The primary outcome of death, MI, or refractory ischaemia at 9 days was similar between groups (non-inferiority, p=0.007). Rates of major bleeding, as well as the composite of the primary outcome and major bleeding at 9 days, were markedly lower with fondaparinux than with enoxaparin (p<0.001). Fondaparinux was associated with a significant reduction in the number of patients with fatal bleeding (p=0.005) and an almost halving of severe bleeding.[45] Anticoagulation crossovers with UFH or baseline creatinine clearance did not affect the bleeding advantage of fondaparinux. The outcome of PCI patients was similar between groups but bleedings were lower and guiding-catheter thrombus formation was more fregment with fondaparinux (0.9% vs. 0.3%). Fondaparinux was associated with a lower number of deaths at 30 and at 180 days. Because mortality was higher among patients with than without bleeding, regardless of the therapy assigned, the mortality benefit of fondaparinux was attributed to its lower associated haemorrhagic risk.[45]

STEMI

The OASIS 6 trial compared fondaparinux or control (placebo or UFH) for ≤8 days (median 45 hours) in patients with STEMI.[29] From day 3 until day 9, all patients received either fondaparinux or placebo. Both strata included subgroups that did or did not receive reperfusion therapy. The results of OASIS 6 can be summarized as follows:

- Fondaparinux over control reduced the primary outcome of death or MI at 30 days from 11.2% to 9.7% (hazard ratio [HR] 0.86, 95% CI: 0.77-0.96; p=0.008). The benefit was apparent as early as 9 days.
- Fondaparinux over control was of benefit for patients without reperfusion (HR 0.80; p=0.03) and those with thrombolysis (HR 0.79; p=0.03)
- Fondaparinux vs. placebo demonstrated fewer deaths/MIs at 30 days and a statistically marginal benefit regarding the rates of major bleedings
- In the fondaparinux vs. UFH stratum of patients, 53% underwent primary PCI and 45% thrombolysis.
- Fondaparinux vs. UFH showed a strong trend for death or MI reduction at 30 days (HR 0.82, 95% CI: 0.66-1.02; p=0.08) and at 180 days (HR 0.77, 95% CI: 0.64-0.93; p=0008) in STEMI patients without primary PCI, and similar rates regarding major or severe bleeding events.
- Fondaparinux vs. UFH showed a strong trend for harm in primary PCI (HR 1.20; p=0.19). In primary PCI, there was a higher rate of guide catheter thrombosis (22% vs. 0% p<0.001) and more total coronary complications in the fondaparinux group (p=0.04) These catheter-related complications were abolished after pre-treatment with UFH.

Collectively, fondaparinux in STEMI appears: 1) superior to placebo in terms of ischaemic complications, whether without reperfusion or post-thrombolysis, without an increased bleeding risk; 2) marginally more effective than and equally as safe as UFH in non-primary PCI patients; and 3) inferior to UFH in primary PCI.[29]

Direct thrombin inhibitors

These anticoagulants exhibit intrinsic activity by binding to thrombin and inhibiting its enzymatic activity. The currently approved direct thrombin inhibitors (DTI) are hirudin, argatroban and bivalirudin.[3] DTI prevent fibrin formation and thrombin-mediated activation of other coagulation factors as well as platelet activation, thereby reducing further thrombin generation. Importantly, DTI can also inactivate fibrin-bound thrombin. The naturally occurring hirudin, which has been isolated from leech saliva, and argatroban, a synthetic arginine-containing molecule, are potent direct thrombin inhibitors.[3] Argatroban, as well as lepirudin (Refludan®) and desirudin (both recombinant hirudins), are licensed for the treatment and prevention of HIT. Bivalirudin is licensed as an

alternative to heparins in patients with ACS undergoing PCI. No specific antidotes exist for these drugs; however haemodialysis or haemoperfusion can remove bivalirudin or argatroban.[3]

Bivalirudin

Bivalirudin (Angiox®), a 20-amino-acid synthetic polypeptide, is a hirudin analogue forming a 1:1 stoichiometric complex with thrombin. Bivalirudin is not inactivated by circulating inhibitors, it does not bind to plasma proteins, does not influence platelet function and is not immunogenic.[3,4] The drug has a plasma half-life of 25 min after IV injection, and 20% of it is excreted via the kidneys. Thus, dose reduction should be considered in patients with moderate to severe renal impairment.

Clinical use of bivalirudin

NSTEACS

A re-analysis of data from an old study of hirulog vs. very high-dose UFH suggested that bivalirudin was associated with lower rates of ischaemia and bleeding complications.[46] Bivalirudin compared with UFH monotherapy in elective or urgent PCI demonstrated similar efficacy and safety.[47] Bivalirudin with provisional GPI vs. UFH + GPI in urgent or elective PCI revealed that in-hospital major bleeding rates were significantly reduced by bivalirudin ($p<0.001$).[48] In the ACUITY trial, patients with moderate-to-high risk NSTEACS were randomised to receive either 1) UFH or enoxaparin + GPI, 2) bivalirudin + GPI, or 3) bivalirudin monotherapy.[49] The study results were similar in the heparins + GPI vs. bivalirudin + GPI groups with regard to efficacy and safety. The results in the heparins + GPI vs. bivalirudin alone groups were similar for ischaemic events (p=NS), but favoured bivalirudin regarding major bleedings and net clinical benefit. There were increased ischaemic complications in bivalirudin patients without clopidogrel pre-treatment before coronary angiography and PCI.[49] In the ISAR-REACT-4 trial, NSTEMI patients undergoing PCI were randomised to receive either abciximab + UFH or bivalirudin with provisional GPI use after clopidogrel pretreatment.[50] The incidence of ischaemic complications was similar in both groups. Rates of major bleeding were 4.6% vs. 2.6% ($p=0.02$). Notably, in a preliminary report outside the setting of ACS, patients at high risk of bleeding who underwent elective transfemoral PCI were randomised to receive either bivalirudin or UFH.[51] The study's primary outcome of major bleeding was 3.3% vs. 2.6% in the bivalirudin vs. UFH group (OR 1.28; 95% CI: 0.58-2.86; $p=0.54$) with no differences in entry- and non-entry-site bleeding episodes. Ischaemic events were similar between groups.[51] Finally, in a preliminary Swedish analysis, UFH monotherapy appeared to reduce 30-day mortality over bivalirudin monotherapy in NSTEACS patients.[52]

Primary PCI

In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, patients undergoing primary PCI received bivalirudin with provisional GPI use or UFH + GPI.[53] The study results were as follows: primary outcome of major bleedings and ischemic events at 30 days (net clinical benefit): RR 0.76; 95% CI: 0.63-0.92; $p=0.005$; major bleeding rates: RR 0.60; 95% CI: 0.46-0.77; $p<0.001$; all-cause mortality: 2.1% vs. 3.1% ($p=0.047$); stent thrombosis: 1.3% vs. 0.3% ($p<0.001$).[53]

In the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial, primary PCI patients received anticoagulation, either in the ambulance or in a non-PCI capable hospital, and randomly received bivalirudin with optional GPI vs. 100 U/kg UFH or enoxaparin with optional GPI (control group).[54] The bivalirudin group received in addition an extended 4-hour 0.25 mg/kg/h infusion. Administration of a GPI was unevenly distributed (70% in the control group and 11% in the bivalirudin group). Half of the study patients were loaded with the newer $P2Y_{12}$ receptor inhibitors. The RR for the primary outcome of death or major, non-CABG related bleeding was 0.60 (95% CI: 0.43-0.82; $p=0.001$). Mortality rates were similar, whereas incident stent thrombosis was 6-fold higher in the bivalirudin compared with the heparin group ($p=0.007$), with two thirds of the patients experiencing reinfarctions. The better primary outcome for bivalirudin was entirely due to lower rates of protocol-defined but not TIMI- or GUSTO-defined major bleedings.[54] This study showed that neither prolonged bivalirudin infusion nor the newer, more potent antiplatelet agents were capable of preventing stent thrombosis. In the How Effective are Antithrombotic Therapies in Primary PCI (HEAT PPCI) trial, patients randomly received either bivalirudin with bailout GPI (in 13% of the patients) or 70 U/kg UFH with bailout GPI (in 15%

of the patients).[55] Novel $2PY_{12}$ receptor inhibitors were given in 89% and the radial access site was selected in 81% of the patients. The primary composite of all-cause mortality, cerebrovascular accident, re-MI or unplanned target lesion revascularisation was 8.7% vs. 5.7% (RR 1.52, 95% CI: 1.1-2.1; p=0.01). All components of the primary end-point were higher in the bivalirudin group, whereas the risk for stent thrombosis (largely acute) was 3.91 (95% CI: 1.6-9.5; p=0.001). The incidence of major bleeding was similar between groups (p=0.59).[55]

In a recent Chinese report, patients with MI eligible for emergent PCI (89% with STEMI with a mean presentation time as late as 6.9 hours) were randomised to bivalirudin monotherapy, 100 U/kg UFH monotherapy, or 60 U/kg UFH + GPI.[56] The primary end-point of ischaemic complications or any bleeding at 30 days was 8.8%, 13.2% and 17% in the 3 groups, respectively (all p<0.05). Ischaemic complications, including acute stent thrombosis, were similar; moderate or severe BARC 2-5 haemorrhages were more frequent in the 2 UFH arms but severe BARC 3-5 bleedings were not different between groups.[56]

Meta-analysis of bivalirudin in comparison with heparins

A recent meta-analysis reported no differences in death or MI rates between bivalirudin and UFH, a UFH dose-dependent reduction in major haemorrhages favouring bivalirudin, and an increase in the frequency of urgent target-vessel revascularisation and acute stent thrombosis in bivalirudin-treated patients.[57] Another pooled comparison showed that a bivalirudin-based regimen increased the risk of MI and stent thrombosis, but decreased the risk of bleeding, with the magnitude of the reduction depending on concomitant GPI use.[58] The latest to date direct comparison meta-analysis in primary PCI confirmed the increased bivalirudin-related ischaemic risk and the increased UFH-associated haemorrhagic potential, with major bleedings being 32% lower for bivalirudin as compared with UFH monotherapy.[59] Adding GPI optimised the treatment efficacy of heparins but compromised safety, whereas bivalirudin monotherapy followed by UFH monotherapy demonstrated the safest profile.[59] However, there remains the issue whether bivalirudin has any bleeding advantage over only 60-70 U/kg UFH, because the pertinent studies to date (with either scheduled[49] or provisional GPI administration[47,51,55]) have yielded very comparable results between the 2 anticoagulants.

Switching

Switching from UFH to bivalirudin resulted in reduced rates of major bleeding and improved cardiac survival.[60,61]

Trends and evolving issues

Considering anticoagulants in ACS, the use of UFH worldwide halved and that of enoxaparin almost doubled from the year 2000 to 2007 (to 24% and to 63%, respectively). Treatment with GPI has remained in the order of 16% and declined to 46% in primary PCI,[62] which is similar to primary PCI trends in the UK.[63] In the US from 2005 to 2009, UFH was most commonly used in PCI for STEMI, but bivalirudin administration rose to 45% in elective PCI patients. Major bleeding declined by 20%, with antithrombotic strategies being associated with roughly half of the reduction in annual bleeding risk.[64] Use of a GPI in patients with STEMI undergoing PCI was slightly less than 60% in the US in 2009,[64] 14% in the HEAT PPCI trial, and ~11% of the ACS patients at the Rio University Hospital.[65] Nevertheless, stent thrombosis on a background of ticagrelor or prasugrel therapy has remained very low. In fact, current practice in most coronary procedures is no longer GPI administration as initial treatment strategy in PCI but rather first the selection of the anticoagulant drug followed by only provisional GPI use, even in primary coronary interventions.

General considerations and drug dosage

- The cost-effectiveness and safety profile of each parenteral anticoagulant should be viewed in the context of the ischaemic vs. bleeding risk relation, as well as of the selected treatment strategy in every patient
- UFH is the only anticoagulant not requiring dose adjustment in chronic kidney disease.
  - IV rather than SC administration is advised.
  - aPTT target: 50-75 s or 1.5-2.0 times control. The therapeutic aPTT range has to be adjusted to the reagent used. Values should be determined at 6 and every 24 hours.
  - ACT use is obsolete in elective PCI, regardless of UFH dose, and in any transradial PCI with 100 U/kg of UFH.
  - ACT use is recommended in POBA, in complicated PCI and in primary ACS-PCI.

  - ACT targets for PCI with UFH ± GPI: 200-250 s,
- UFH DOSAGE:
  - NSTEACS or nonreperfused STEMI: 60-70 U/kg up to 5000 U bolus + 12-15 U/kg/hour (up to 1000 U/kg/hour).
  - Thrombolysed STEMI: 60 U/kg up to 4000 U bolus + 12 U/kg/hour (up to 1000 U/kg/hour).
  - Transfemoral PCI as monotherapy: 70 U/kg bolus (up to 85 U/kg in fondaparinux pretreatment) with ACT control in ACS-PCI.
  - Transradial PCI as monotherapy: up to 100 U/kg bolus in patients at high ischaemic risk
  - PCI with a GPI: 60 U/kg bolus.
- ENOXAPARIN DOSAGE:
  - 1 mg/kg/12 hours SC (for patients >75 years 0.75 mg/kg/12 hours; bolus administration should be omitted).
  - In thrombolysed STEMI: 30 mg IV bolus, then as above with total first day dose 100 mg/24 hours (for patients >75 years, 75 mg/24 hours).
  - In PCI (including primary PCI): 0.5 mg/kg bolus (regardless of GPI use).
  - In PCI following SC regimen: 0.3 mg/kg additional bolus >8h after the last injection.
  - Creatinine clearance <30 mL/min: 1.0 mg/kg once daily (UFH should be preferred).
- FONDAPARINUX DOSAGE:
  - 2.5 mg/24 hours SC.
  - In thrombolysed STEMI: 2.5 mg IV bolus, then SC dose 24h later.
  - Creatinine clearance <30 mL/min: fondaparinux should not be used (UFH should be preferred).
- BIVALIRUDIN DOSAGE FOR PCI:
  - 0.75 mg/kg bolus, 1.75 mg/kg/hour infusion during the procedure without additional infusion following PCI.[66]
  - Creatinine clearance <30 mL/min: 1 mg/kg/hour infusion (UFH should be preferred).
- PRIMARY PCI IN PATIENTS UNDER ORAL ANTICOAGULATION:
  No data are available. The operators should balance between antidote availability of UFH and bivalirudin's lower bleeding risk.[67]
  Anticoagulation dose recommendations:
  1. Usual dose at the trough of action of new oral anticoagulants or when the vitamin K antagonist (VKA) therapy is considered insufficient.
  2. No anticoagulant administration at the peak of action of new oral anticoagulants or when the VKA therapy is considered of sufficient or high level.
  3. Bivalirudin in usual dose or UFH 50 U/kg in ambiguous cases (e.g. steady-state plasma levels of new oral anticoagulants or anticipated international normalized ratio [INR] of > 1.6 but < 2.5).
  4. UFH in more liberal dosage in transradial primary PCI.

Heparin-induced thrombocytopenia (HIT)

- We recommend awareness of possible HIT by considering the magnitude and timing of thrombocytopenia, as well as the occurrence of thromboembolic complications and exclusion of other causes for platelet count drop (4Ts score).
- The absence and presence of antigen-specific antibodies in plasma have high negative and low positive predictive value, respectively.
- In HIT with thrombotic complications, we suggest argatroban or lepirudin or danaparoid over other non-heparin anticoagulants, and argatroban if renal function is impaired.
- If urgent surgery is scheduled, bivalirudin is the preferred anticoagulant.
- In severe thrombocytopenia, platelet transfusions may be administered only if bleeding risk is high or during the performance of an invasive procedure.
- Overlap with initially low dose VKAs should be performed only after recovery from thrombocytopenia and VKA therapy should be maintained for 3 months in HIT with thrombosis and for 1 month for HIT without thrombotic complications.

Acute coronary syndromes

NSTEACS, nonreperfused STEMI & thrombolysed STEMI (Figure 2)

- In NSTEACS, it is reasonable to suggest fondaparinux (to reduce bleeding complications over enoxaparin) or enoxaparin up to hospital discharge (to reduce reinfarctions over UFH), rather than UFH for >48 hours, especially when an early invasive strategy (i.e. within 24-72 hours) has not been planned.
- In thrombolysed or non-reperfused STEMI, it is

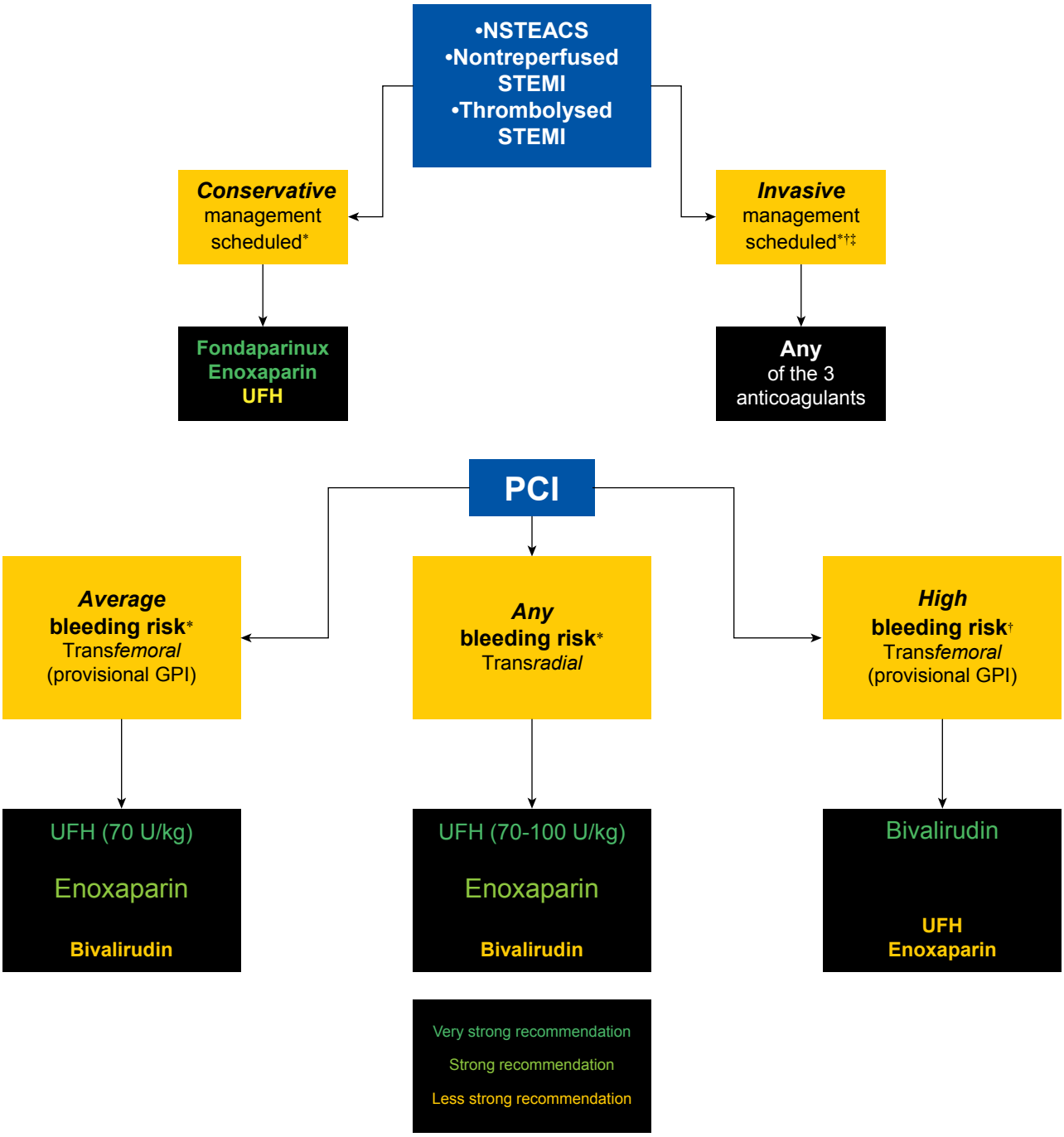

Figure 2. Algorithm of parenteral anticoagulant use in acute coronary syndromes and percutaneous coronary intervention (PCI).

*Without history of heparin-induced thrombocytopenia for heparins. †Without severe chronic kidney disease for non-UFH anticoagulants. ‡Early, elective coronary angiography, i.e. within 1-3 days is possible. NSTEACS – non ST-elevation ACS; STEMI – ST-elevation myocardial infarction; UFH – unfractionated heparin; GPI – platelet glycoprotein IIb/IIIa receptor inhibitors.

reasonable to suggest fondaparinux or enoxaparin over UFH and over no anticoagulant up to hospital discharge in conservatively treated patients.

- It is reasonable to suggest any of the above 3 anticoagulants in whom an invasive strategy is planned.
- Before thrombolysis, the increased enoxaparin bleeding propensity over that of UFH has to be balanced against the possible coronary angiographic availability within the first 24-72 hours post-thrombolysis.

PCI (Figure 2)

- It is reasonable to suggest 70 U/kg UFH or enoxaparin with provisional GPI over bivalirudin with provisional GPI in transfemoral PCI patients without high bleeding risk, given the cost difference and probably unfavourable ischaemic vs. bleeding risk relation of bivalirudin.
- It is reasonable to suggest bivalirudin over UFH or enoxaparin with provisional GPI in transfemoral PCI patients with a high bleeding risk.
- It is reasonable to suggest 70-100 U/kg UFH or enoxaparin with provisional GPI use over bivalirudin in transradial PCI patients, given the cost difference and probably negligible bleeding risk difference between the 2 drug regimens.
- We advice against the administration of fondaparinux in any PCI.

Transradial coronary angiography and interventions, TAVI

- It is reasonable to suggest >5000 U of UFH (or >50 U/kg) for transradial coronary angiography.
- The highest recommended UFH dose (up to 100 U/kg with, or up to 70 U/kg without GPI) is possible in transradial PCI, if the ischaemic risk is considered high (e.g. primary PCI).
- It is reasonable to suggest a target ACT of ≥300 s throughout the TAVI procedure. However if bleeding complications occur at the access site, reversal of UFH can be performed with protamine sulphate.

Anticoagulant switching

- Switching from UFH to bivalirudin is possible and safe. Bivalirudin should be initiated >30 minutes after the last UFH dose or just before PCI.
- Switching from enoxaparin should be avoided, unless UFH or bivalirudin is administered >8 hours after the last enoxaparin dose.
- Switching from fondaparinux to 85 U/kg of UFH (60 U/kg with a GPI) is recommended when PCI is performed.
- Any switching is possible >8h for enoxaparin, >2h for UFH and >1h for bivalirudin.

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