

## Review Article

# Current Therapy of Non-ST-Elevation Acute Coronary Syndromes

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**A**cute coronary syndromes (ACS) include unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation MI (STEMI). Each year in the US, approximately 1,360,000 patients are admitted for ACS, of which 810,000 have an MI and the remainder UA. Approximately two thirds of patients with MI have NSTEMI and the rest have STEMI.<sup>1</sup> Worldwide, more than 3 million people each year are estimated to have a STEMI and more than 4 million have an NSTEMI.<sup>2</sup> Hospital mortality is higher in patients with STEMI but the long-term mortality is higher in patients with non-STE ACS.<sup>3</sup> Thus, optimal management of NSTEMI-ACS is important in this clinical setting. This review reflects recent evidence in the context of the relevant guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC).<sup>4-6</sup>

## Supportive measures

**Oxygen** should be administered when the arterial saturation is <90%. **Nitroglycerin**, sublingually or as a buccal spray (0.4 mg), can be given for pain relief every 5 min for a total of 3 doses. If the pain persists or hypertension or heart failure are present, IV nitroglycerin can be given (initial dose 5-10 µg/min with 10 µg/min in-

crements until the systolic blood pressure falls below 100 mm Hg), but is contraindicated if sildenafil has been taken within the previous 24 (or tadalafil in the previous 48 h). **Morphine** is used for pain relief, although there are observational indications that it may increase mortality in ACS.<sup>7</sup> Because of the increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use, **non-steroidal anti-inflammatory drugs** (NSAID), whether nonselective or cyclooxygenase (COX)-2 selective agents, should be discontinued at the time a patient presents with UA/NSTEMI.

**Beta-blockers** should be initiated within the first 24 h in patients who do not have signs of acute heart failure or a low-output state, increased risk for cardiogenic shock, or other relative contraindications to beta blockade (PR interval >0.24 s, second or third degree heart block, active asthma, or reactive airway disease). Beta-blockers reduce the incidence of recurrent ischemia and subsequent MI. IV beta blockade may also be considered in the absence of contraindications. Oral therapy should be continued indefinitely, especially in patients with reduced left ventricular function. In the presence of recurrent symptoms, or Prinzmetal variant angina, or in patients in whom beta-blockers are contraindicated, a non-dihydropyridine calcium chan-

nel blocker (e.g. **verapamil** or **diltiazem**) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications. Immediate release dihydropyridines are contraindicated in the absence of a beta-blocker. **Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers** should be administered orally within the first 24 h probably to all patients and especially to those with pulmonary congestion or a left ventricular ejection fraction  $\leq 0.40$ , in the absence of hypotension (systolic blood pressure  $< 100$  mmHg or  $< 30$  mmHg below baseline) or other contraindications.

### Antiplatelets

**Aspirin** should be administered as soon as possible and then indefinitely, unless there is a history of documented allergy or active bleeding. A loading dose of 162-325 mg (or 250-500 mg bolus IV) followed by 75-162 mg/day should be given indefinitely. Aspirin mainly acts by irreversibly inhibiting platelet COX-1. The effects of aspirin are only reversed when new unaffected platelets enter the circulation, which occurs every 7 to 14 days. Aspirin also inhibits prostacyclin production in gastric endothelial cells and therefore carries a slightly greater risk for gastric ulcer formation than the P2Y<sub>12</sub> inhibitors. A proton pump inhibitor should be added to the treatment of patients with a history of duodenal ulcer or gastrointestinal bleeding. In patients at high risk for gastrointestinal ulceration, the use of prophylactic proton pump inhibition with aspirin is safer than clopidogrel alone without a proton pump inhibitor.

### P2Y<sub>12</sub> adenosine diphosphate receptor blockers

**Thienopyridines** (ticlopidine, clopidogrel and prasugrel) are irreversible P2Y<sub>12</sub> receptor blockers. **Ticagrelor** is a non-thienopyridine reversible P2Y<sub>12</sub> receptor blocker. Ticlopidine, the first of the adenosine diphosphate (ADP) receptor blockers, is rarely used in practice because of uncommon but serious side effects (e.g. thrombocytopenia purpura and neutropenia due to bone marrow suppression). Clopidogrel and prasugrel are “prodrugs” that require activation in the liver via the cytochrome P450 system. Ticagrelor is not a prodrug, but requires twice-daily dosing owing to its short half-life. Clopidogrel or prasugrel (if  $< 75$  years of age,  $> 60$  kg, no prior stroke/TIA or increased bleeding risk) are recommended by the

ACC/AHA 2011 Guidelines on UA/NSTEMI.<sup>5</sup> The ESC 2011 guidelines on UA/NSTEMI recommend ticagrelor or clopidogrel unless the patient proceeds to intervention, when ticagrelor and prasugrel (P2Y<sub>12</sub>-naïve patients and especially diabetics with no high risk of bleeding) are preferred.<sup>6</sup> There is no antidote for P2Y<sub>12</sub> inhibitors.

**Clopidogrel** (loading dose 300-600 mg po followed by 75 mg/day, starting on presentation) is recommended for up to one year (CURE trial).<sup>8</sup> A higher dose of 150 mg/daily may be used for the first 6 days in patients who have had a loading dose for percutaneous coronary intervention (PCI).

Binding of metabolized clopidogrel to ADP receptors on the platelet surface is catalyzed mainly by the cytochrome enzyme CYP2C19. Loss-of-function polymorphisms in the gene encoding for CYP2C19 are associated with a reduced response to clopidogrel (2-14% of patients) and a potentially increased risk of adverse cardiovascular events.<sup>9,10</sup> However, among patients with acute coronary syndromes or atrial fibrillation, the effect of clopidogrel as compared with placebo has been found to be consistent, irrespective of CYP2C19 loss-of-function carrier status.<sup>11,12</sup> Other genetic variations, such as the ABCB1 3435 TT genotype, may also affect the pharmacokinetics and clinical efficacy of clopidogrel.<sup>12</sup> Platelet function assays can measure the effect of ADP or P2Y<sub>12</sub> activation on platelet aggregation, receptor expression, or the level of intracellular molecules (e.g. vasodilator-stimulated phosphoprotein phosphorylation), thereby directly or indirectly measuring the platelet inhibitory effect of clopidogrel. There is now insufficient evidence to recommend either routine genetic or platelet function testing at the present time. Higher loading (600 mg twice) and maintenance (150 mg) doses of clopidogrel or new inhibitors (prasugrel or ticagrelor) are the alternatives in high-risk patients who have a poor response (i.e. patients who have stent thrombosis while taking clopidogrel), respectively.

**Omeprazole** (and especially **lansoprazole**) are proton-pump inhibitors that also inhibit the cytochrome enzyme CYP2C19. **Pantoprazole**, which inhibits the enzyme less than omeprazole, should lessen the risk when taken 4 h after clopidogrel.<sup>13</sup> However, in clinical trials the combination of clopidogrel with proton-pump inhibitors has not increased cardiac events.<sup>14,15</sup> Thus, the combination of clopidogrel with a proton-pump inhibitor is considered safe. Similarly, a diminished pharmacodynamic response to clopidogrel has been observed when it is co-ad-

ministered with lipophilic statins and calcium channel blockers, but in clinical practice no increased cardiovascular risk has been demonstrated with these combinations.<sup>16,17</sup> Proton-pump inhibitors seem to be associated with increased risk for adverse cardiovascular outcomes after discharge, regardless of clopidogrel use for myocardial infarction.<sup>18</sup> Clopidogrel metabolites can inhibit the enzymatic activity of cytochrome P4502C9 and lead to increased plasma levels of NSAIDs.

Clopidogrel hypersensitivity is manifested as generalized rash and is caused by a lymphocyte-mediated delayed hypersensitivity in most patients. This can be managed with oral steroids (prednisone 30 mg bd for 5 days with gradual tapering over the next 15 days, and diphenhydramine 25 mg every 8h for pruritus) without clopidogrel discontinuation.<sup>19</sup> Allergic cross-reactivity with ticlopidine, prasugrel, or both is present in a significant number of patients with clopidogrel hypersensitivity.

**Prasugrel** is more consistent than clopidogrel, with a faster onset of action and fewer potential drug interactions. It has been shown to be better than clopidogrel in patients with non-STE ACS, particularly in those with diabetes, for reducing adverse cardiac events and late stent thrombosis, but it can increase major bleeding (TROPON-TIMI 38 trial).<sup>20</sup> The rate of other adverse effects in the TRITON study was similar with prasugrel and clopidogrel. Thrombocytopenia occurred at the same frequency in each group (0.3%), while neutropenia was less common with prasugrel (<0.1% vs. 0.2%,  $p=0.02$ ). Concerns have been raised regarding a possible increased risk of cancer with prasugrel. Platelets inhibit angiogenesis through the activity of platelet factor-4 and facilitate tumor cell adhesion and trapping in capillaries through expression of P-selectin. Disruption of tumor-platelet aggregates by chronic profound oral platelet inhibition may cause extensive dissemination of initially silent tumors. A recent FDA report concluded that cancer risks after prasugrel are higher in women and after 4 months of therapy, at least for solid, highly metastatic cancers.<sup>21</sup> Further data are needed for certain conclusions. Prasugrel can be used instead of clopidogrel in patients undergoing PCI, in a 60 mg loading dose followed by 10 mg/daily, or 5 mg if the patient weighs <60 kg. It is not recommended in patients aged >75 years or if the risk of coronary artery bypass grafting (CABG) is high. It is contraindicated in patients with a history of transient ischemic attacks or stroke.

**Ticagrelor** is a cyclopentyltriazolopyrimidine, and is a reversibly binding P2Y<sub>12</sub> inhibitor with a plasma half-life of <12 h. It has been shown to reduce mortality in ACS compared to clopidogrel, without increased bleeding (PLATO trial).<sup>22</sup> Ticagrelor was associated with similar total major bleeding but increased non-procedure-related major bleeding. Ticagrelor increases the levels of drugs metabolized through CYP3A, such as simvastatin, whilst moderate CYP3A inhibitors, such as diltiazem, increase the levels and reduce the speed of offset of the effect of ticagrelor. Ventricular pauses, mostly in the acute phase of ACS due to sinus node suppression, and mild dyspnea without any adverse effect on cardiac or pulmonary function may be seen and are believed to be adenosine-mediated.<sup>23</sup> They are of no clinical significance.<sup>24</sup> A lack of efficacy among US patients and a probable reduced effect in co-administration with high dose aspirin (325 mg as opposed to 75 mg, attributed to increased vascular resistance through inhibition of cyclooxygenase within blood vessels) are probably not matters of concern.<sup>25,26</sup> A slightly greater increase in serum creatinine was seen in the PLATO trial with ticagrelor compared with clopidogrel, but the difference was no longer apparent 1 month after cessation of treatment. Rates of gastrointestinal disturbance and rash are similar with ticagrelor compared to clopidogrel.<sup>6</sup> Ticagrelor is given as a loading dose of 180 mg po, followed by 90 mg twice daily.

## Anticoagulants

### Heparin

Either **enoxaparin** or **unfractionated heparin** (IV for 48 h) is given as soon as possible. **Unfractionated heparin** (UFH) is a heterogeneous group of negatively charged, sulfated glycosaminoglycans (molecular weight 3000 to 30,000 Da) from animal sources. Low-molecular-weight heparins (LMWH; molecular weight, 2000 to 10,000 Da) are produced from unfractionated heparin by chemical or enzymatic processes. UFH activates antithrombin through the formation of a heparin-antithrombin complex that inhibits other coagulation factors. The protein-binding properties of heparin are mainly responsible for the lack of linear relationship between dose, activated partial thromboplastin time (aPTT), and clinical outcomes. There is a variable therapeutic response depending on age, weight, and renal function, and also a requirement for monitoring of aPTT. Elimination

of the drug is mainly by the kidneys (and the reticulo-endothelial system) and the half-life is approximately 6 hours.

- *Dose for conservative therapy:* IV bolus 60 U/Kg (max 5000 U) followed by infusion of 12 U/kg/h (max 1000 U/h) to maintain aPTT 1.5-2 times control (50-70 s) for 48 h.
- *Dose for PCI:* Target ACT 200-250 s when IIb/IIa are also given (heparin bolus of 60-70 U/kg if not initially given) or ACT 250-300 s without IIb/IIIa (heparin bolus of 100-140 U/kg if not initially given). No additional treatment after PCI.

**Protamine sulfate** is an effective antidote (1 mg /100 u heparin IV). Very rarely allergic shock may occur with its use.

**LMWH** (enoxaparin, dalteparin, fraxiparin) are specific inhibitors of thrombin and factor Xa with high bioavailability. When given subcutaneously, they provide more consistent anticoagulation, avoiding the need for monitoring, and are associated with a lower risk for heparin-induced thrombocytopenia than are UFH. Disadvantages are the only partial reversibility by protamine, renal excretion, and reduced efficacy against the contact activation pathway (factors XIa and XIIa) that contributes to thrombosis on catheter tips, stents, and filters.<sup>27</sup> Enoxaparin reduces death and myocardial infarction compared to unfractionated heparin in non-STE ACS.<sup>28</sup>

- *Dose for conservative therapy:* IV bolus of 30 mg followed 15 min later by 1 mg/kg/12 h SC provided the serum creatinine is <2.5 mg/dL in men and <2.0 mg/dL in women, for duration of hospitalization up to 8 days. Therapeutic dosing should achieve an anti-Xa level of 0.6-1 IU/ml, but this is seldom measured. If creatinine clearance is <30 ml/min, the dose is 1 mg/kg/24 h. For patients >75 years of age, the initial intravenous bolus may be eliminated and the subcutaneous dose reduced to 0.75 mg/kg every 12 hours.
- *Dose for PCI:* IV bolus of 0.5-0.75 mg/kg, or 0.3 mg/kg if the last SC dose was given >8h. No additional dose if last SC dose was given <8 h. If the procedure is prolonged (>2h) an additional IV dose of 0.25 mg/kg may be given. No additional treatment after PCI.

### Direct thrombin inhibitors

**Bivalirudin** is a reversible direct thrombin inhibitor with additional mild antiplatelet activity. It has

a very short half-life, and is less likely to accumulate in patients with renal insufficiency. It can be used as an alternative to heparin if an invasive strategy is planned. In moderate- and high-risk patients, bivalirudin alone has a similar ischemic benefit to either unfractionated heparin or enoxaparin with a IIb/IIIa antagonist, but with a reduction in major bleeding (ACUITY).<sup>29</sup>

- *Dose for conservative therapy:* 0.1 mg/kg bolus, 0.25 mg per kg/h infusion for up to 72 h.
- *Dose for PCI:* 0.5 mg/kg bolus, and infusion of 1.75 mg/kg/h if initial medical dosing was given, otherwise 0.75 mg/kg bolus, 1.75 mg/kg/h infusion until the end of PCI or up to 4 h later.

If the creatinine clearance is <30 mL/min, reduction of the infusion rate to 1.0 mg/kg/h should be considered. If a patient is on hemodialysis, the infusion should be reduced to 0.25 mg/kg/h. No reduction in the bolus dose is needed.

### Direct factor Xa inhibitors

**Fondaparinux** reduces major bleeding and improves clinical outcomes compared to enoxaparin, with or without a IIb/IIIa inhibitor (OASIS-5).<sup>30</sup> In patients managed conservatively it is preferred over heparin, especially when there is a high risk of bleeding. Fondaparinux is the longest acting of the anticoagulants, with a half-life approaching 24 hours through renal clearance. It is contraindicated in patients with creatinine clearance <30 mL/min, but a much lower risk of bleeding complications was observed in OASIS-5 with fondaparinux when compared with enoxaparin, even in patients with severe renal failure. It is not recommended when an invasive approach is planned.

- *Dose for conservative therapy:* 2.5 mg IV bolus followed by 2.5 mg SC once daily for duration of hospitalization (up to 8 days).

If PCI is performed additional UFH heparin is needed (50-60 U/kg bolus) (risk of catheter thrombosis).

### Glycoprotein IIb/IIIa antagonists

Glycoprotein IIb/IIIa receptor inhibitors block the final common pathway of platelet activation. **Abciximab** is a Fab fragment that targets the glycoprotein IIb/IIIa receptor and may be specifically used

in percutaneous coronary intervention. The small-molecule inhibitors **eptifibatide** and  **tirofiban** are short-acting and require dose adjustment in patients with poor renal function. In elderly patients lower efficacy and higher rates of bleeding are seen.

IIB/IIIa antagonists initiated early after admission reduce death and myocardial infarction but increase the risk of bleeding.<sup>31</sup> They may be used in patients with elevated cardiac enzymes and/or recurrent ischemia and in patients proceeding to angiography and PCI, especially in the absence of clopidogrel preloading or in the presence of visible thrombus. Their routine use in patients treated medically is not recommended. The benefit of glycoprotein IIB/IIIa inhibition appears to be greatest for high risk patients with elevated troponin, diabetes, and recurrent angina. Patients treated medically and who develop recurrent ischemia, heart failure or serious arrhythmias should be referred for urgent coronary angiography. In these patients IIB/IIIa antagonists or clopidogrel loading are added to aspirin. The main risk is bleeding, usually at the site of the arterial puncture. They should be given with caution if urgent CABG is anticipated. In patients who are already receiving bivalirudin, and if at least 300 mg of clopidogrel were given at least 6 h earlier, and an invasive strategy is planned, upstream administration of a IIB/IIIa antagonists should be omitted.

Reversibility of action is slow with abciximab (48h to 1 week), and faster with tirofiban (4-8 h) and eptifibatide (2-4 h).

- *Abciximab dose:* IV bolus 0.25 mg/kg followed by infusion of 0.125 µg/kg/min (max 10 µg/min) for 12 h after PCI. There are no specific recommendations for the use of abciximab or for dose adjustment in the case of renal failure. Careful evaluation of hemorrhagic risk is needed before using the drug in the case of renal failure.
- *Eptifibatide dose:* IV bolus 180 µg/kg followed by infusion of 2.0 µg/kg/min (for 18-24 h after PCI); reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min. As 50% of eptifibatide is cleared through the kidneys in patients with renal failure, precautions must be taken in patients with impaired renal function (creatinine clearance <50 mL/min). The infusion dose should be reduced to 1 mg/kg/min in such patients. The dose of the bolus remains unchanged at 180 mg/kg. Eptifibatide is contraindicated

in patients with creatinine clearance <30 mL/min.

- *Tirofiban dose:* IV infusion of 0.4 µg/kg/min for 30 min followed by infusion of 0.1 µg/kg/min (for 18-24 h after PCI); reduce infusion by 50% in patients with estimated creatinine clearance <50 mL/min. Dose adaptation required in patients with renal failure. 50% of the dose only if creatinine clearance <30 mL/min.

## Warfarin

Warfarin, although not specifically indicated for ACS, is often used concurrently for other indications, such as atrial fibrillation, mechanical valves, left ventricular thrombus, or deep venous thrombosis. Warfarin is a racemic mixture of isomers that inhibits synthesis of vitamin K-dependent coagulation factors. The effective dose of warfarin varies significantly among individuals, due to genetic variations in its receptor, metabolism via the cytochrome P450 system, and interactions with other drugs, vitamins, and green vegetables. Warfarin use alone increases the risk of bleeding to 13% per year, and risks are highest among new users and the elderly. Combinations of warfarin, aspirin, and clopidogrel carry a more than 3-fold higher risk than warfarin monotherapy.<sup>32</sup>

Patients with atrial fibrillation on oral anticoagulant treatment are often bridged with unfractionated heparin or low molecular weight heparin if they need coronary angiography or PCI.

The following recommendations are useful:<sup>33</sup>

1. Observational studies suggest that coronary angiography or PCI can be safely performed without interrupting warfarin, and may be associated with a lower rate of complications compared with bridging therapy to heparin. There is no need for additional heparin in patients who undergo PCI while therapeutic on warfarin (international normalized ratio 2-3). Aspirin and clopidogrel should be administered prior to the procedure when PCI is performed in a patient on warfarin. The use of proton-pump inhibitors may help reduce the risk of bleeding.
2. The use of platelet glycoprotein IIB/IIIa inhibitors increases the risk of bleeding in patients on warfarin 3- to 13-fold and the routine use of these agents should be avoided.
3. Combinations of aspirin and warfarin do not

provide sufficient protection against the risk of stent thrombosis. Patients undergoing stent-based PCI should be treated with triple therapy consisting of aspirin, clopidogrel, and warfarin. This combination is associated with an increased risk of bleeding, and the use of bare-metal stents should be considered in these patients to limit the duration of triple therapy. In patients who need long-term oral anticoagulation, the use of drug-eluting stents should be restricted to patients at very high risk of restenosis (long lesions, small vessels, diabetes). Alternative therapies (CABG, medical therapy, bare-metal stents) should be considered before implanting drug-eluting stents in a patient who needs long-term oral anticoagulation.

4. There are limited data on the safety of cardiac surgery in patients who are on warfarin. Currently, these patients are bridged with heparin prior to surgery. In the need of emergent CABG, fresh frozen plasma and vitamin K may be used to reduce the risk of bleeding.

### Coronary intervention

Most (FRISC II, TACTICS-TIMI 18, RITA 3),<sup>34-36</sup> although not all (TIMACA, ICTUS)<sup>37,38</sup> randomized trials have provided evidence in favor of an invasive strategy compared to conservative medical therapy in non-STE ACS. Overall, the invasive strategy provides better long-term outcomes.<sup>39,40</sup> This is particularly true in high risk patients (i.e. elevated cardiac enzymes, ST-T changes, hemodynamic or electrical instability, LVEF<0.40, high TIMI or GRACE risk score, diabetes mellitus, renal failure, and recurrent angina), whereas in low risk patients, and especially women,<sup>41</sup> conservative management with a view to intervention if indicated can be adopted. The optimal timing of coronary angiography and subsequent intervention if indicated – i.e. immediately after admission or after pre-treatment with optimal medical therapy including potent antiplatelet agents – is also debated. Delayed catheterization has been thought to allow plaque passivation by pre-treatment with optimal antithrombotic medication, and avoidance of adverse outcomes, perhaps due to embolic phenomena, by early intervention. It seems that very early angiography (<14 h), with a view to PCI if indicated, is superior to a strategy of preceding anticoagulation and subsequent intervention in patients with non-STE ACS. It reduces residual ischemia and the duration of hos-

pital stay and may also reduce complications, such as bleeding, and major events (death, MI, or stroke).<sup>42</sup> Thus, current guidelines suggest that in high-risk, unstable patients, as well as patients with chronic renal failure, intervention within 24 hours is preferred, while either an early or a delayed approach may be adopted in other patients.

Despite an increased risk for major bleeding in patients older than 75 years of age, a routine early invasive strategy can significantly improve ischemic outcomes in elderly patients with unstable angina and NSTEMI.<sup>43</sup> Care is needed due to the increased risk of bleeding and possibly concurrent renal dysfunction in this group. Tight glycemic control to achieve normoglycemia is no longer recommended.<sup>6</sup> Instead, insulin infusion to maintain glucose levels <189 mg/dl while avoiding hypoglycemia should be preferred. An early invasive strategy is recommended for diabetic patients with non-STE ACS. Diabetic patients with non-STE ACS may receive intravenous glycoprotein IIb/IIIa inhibitors as part of the initial medical management, which should be continued through the completion of PCI. This is no longer recommended as a Class I indication. An invasive strategy, with preparatory hydration and low doses of contrast media is reasonable in patients with mild (stage II) and moderate (stage III) chronic kidney disease, but no data exist for patients with advanced disease (stages IV and V). In pregnant women, an invasive strategy is indicated in high risk patients (IIa-C, ESC).<sup>44</sup>

### Summary of recommendations for antiplatelets/anticoagulants

**In stable patients selected for medical therapy**, aspirin, a P2Y12 receptor blocker, and enoxaparin or preferably fondaparinux are given. If the patient is stable, a stress test should be performed. If, after the test, the patient is classified as low risk, enoxaparin, or preferably fondaparinux, are continued for the duration of hospitalization (up to 8 days) and IIb/IIIa inhibitors are discontinued if given. Aspirin is given indefinitely, and clopidogrel for at least one month and ideally up to one year.

**In patients selected for PCI**, aspirin, clopidogrel and enoxaparin are continued, and a IIb/IIIa antagonist may be initiated in high-risk patients. Alternatively, bivalirudin may be given instead of the combination of enoxaparin and a IIb/IIIa (IIa-B, ESC). Bivalirudin is also preferred over enoxaparin, and a

IIB/IIIa by the ACC/AHA, if at least 300 mg of clopidogrel have been given at least 6 h earlier (IIa-B). Enoxaparin and IIB/IIIa or bivalirudin may be discontinued after PCI in stable, uncomplicated cases. Drug-eluting stents reduce target lesion revascularization, but not mortality or the risk of MI compared to bare-metal stents.<sup>45</sup> The rate of recurrent events in patients undergoing PCI is 20% at 3 years. Half of these events are associated with angiographically mild (<70% stenosis) non-culprit lesions.<sup>46</sup> In patients undergoing PCI, the Syntax Score is an independent predictor of the 1-year rates of death, cardiac death, MI, and target vessel revascularization.<sup>47</sup>

**In patients in whom CABG is indicated** after angiography, aspirin and UFH are continued. Clopidogrel should be ideally stopped 5 days and prasugrel 7 days before CABG if this is possible, although, if needed, CABG can also be performed in patients on clopidogrel.<sup>48</sup> Enoxaparin should be stopped 12-24 h, fondaparinux 24 h, and bivalirudin 3 h before the procedure and replaced by UFH (Class I-B, ACC/AHA). IIB/IIIa inhibitors (eptifibatide or tirofiban) are discontinued 4 h before surgery (abciximab requires a much longer time, at least 48h).

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