ACUTE CORONARY SYNDROMES: THERAPY

Initial Therapy

Oxygen. Oxygen (4-5 l/min) should be administered only when saturation is <90% (Tables 1 and 2).[1] Oxygen, and especially at high rates of 8 l/min, should be avoided in normoxic patients due to potential of increased myocardial injury (AVOID, and DETO2X-AMI trials).[2, 3]

Morphine. Is used for pain relief, although there are observational indications that it may increase mortality in ACS.[4] Doses are 2-8 mg IV repeated at 5-15 min intervals, or diamorphine (5 mg IV, causes less nausea). Administration of morphine appears to delay the antiplatelet effects of newer P2Y12 inhibitors in the hours after primary PCI, perhaps due to delayed absorption.[5, 6]

Beta blockers IV may be administered at the time of presentation of ACS in the absence of contraindications. The use of early IV beta blockers in acute MI reduces the risks of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock, especially during the first day or so after admission.[7] IV intravenous metoprolol very early in STEMI reduced the size of infarction,[8] while before PCI it reduced the incidence of malignant arrhythmias and was not associated with an increase in adverse events.[9] Contraindications are mainly patients with Killip class ≥ III, hypotension (systolic BM <120 mm Hg), PR interval > 0.24 s, second or third degree heart block, and active asthma (COPD is not a contraindication).

Nitroglycerin. Sublingually or as a buccal spray can be given for pain relief. If the pain persists or hypertension or heart failure are present, IV nitroglycerin (initial dose 5-10 mcg/min with 10 mcg/min increases until the systolic BP falls below 100 mm Hg) may be indicated. Contraindicated if sildenafil has been taken within the previous 24 (or tadalafil the previous 48 h). In the acute phase of STEMI, no evidence supports the use of nitrates or calcium antagonists in the acute phase of MI.

Standard Medical Therapy for ACS

All patients should receive:

- ***aspirin (unless if there is true aspirin allergy),***
- ***a $P2Y_{12}$ inhibitor such as ticagrelor or prasugrel (for PCI), or clopidogrel (for fibrinolyisis or if tigagrelor and prasugrel are contraindicated),***
- ***an antithrombin agent* such as *enoxaparin or unfractionated heparin or bivalirudin or fondaparinux (if PCI is not anticipated),***
- ***a statin or other lipid-lowering drug,***

- ***a beta blocker (if not contra-indicated).***

Antiplatelets and Anticoagulants

Specific recommendations on antiplatelet and anticoagulant therapy of ACS is provided in Tables 3-5, Figures 1-3, and Table 6 and Figure 4.

Aspirin

It should be administered as soon as possible and then indefinitely unless if there is a history of documented allergy, or active bleeding. A loading dose of 162-325 mg po (ACC/AHA), or 150-300 mg po or 75-250 mg IV (ESC), followed by 75-100 mg/day po, should be given indefinitely. Higher doses of aspirin are no more recommended following stent implantation, and in a posthoc analysis of the TRANSLATE-ACS trial, maintenance dose of 325 mg of aspirin was not associated with lower risk of MACE, but was associated with an increased risk of minor bleeding events.[10]

Aspirin mainly acts by irreversibly inhibiting platelet cyclooxygenase 1 (COX-1), and decreasing synthesis of thromboxane A^2 which aids in platelet aggregation (Figure 1). In cells with a nucleus, COX can be regenerated. Because platelets have no nucleus, COX-1 cannot be reproduced and is permanently inhibited. This leads to a prolonged antithrombotic effect lasting several days after a single dose until enough new platelets have been produced to restore normal function of the thrombotic system. 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 $P2Y_{12}$ inhibitors. A *proton pump inhibitor* should be added to patients with a history of duodenal ulcer or GI bleeding, age >65 years or concurrent use of anticoagulants or steroids. In patients at high risk for gastrointestinal ulceration, the use of prophylactic proton pump inhibition (PPI) with aspirin is safer to clopidogrel alone without a proton pump inhibitor. Patients on prolonged PPI therapy, ie more than two years and with more than one pill a day, should be monitored for B12 deficiency.[11] Aspirin resistance is extremely rare; pseudoresistance, reflecting delayed and reduced drug absorption, may complicate enteric coated but not immediate release aspirin.[12] The concomitant administration of some NSAIDs such as ibuprofen (but not diclofenac or paracetamol) prevent the irreversible platelet inhibition induced by low-dose aspirin and may limit its cardioprotective effects.[13] If an NSAID is necessary, alternatives such as diclofenac or paracetamol or a selective COX-2 inhibitor like celecoxib or naproxen may be considered, as they have a lesser impact on aspirin's antiplatelet activity.[13, 14] However, the combination of NSAIDs and aspirin can increase the risk of gastrointestinal adverse events.

Aspirin hypersensitivity (has a reported prevalence of 0.6-2.5% in the general population, but data are difficult to interpret due to inconsistent histories and frequent

mislabelling of adverse effects.[15] When documented after a detailed personal history, desensitization may be accomplished in outpatient clinics by oral aspirin challenges with escalating doses every 3 h of 30, 60, and 100 mg, and 150, 325, and 650 mg the next day.[15]

$P2Y_{12}$ receptor blockers

Added to aspirin or used instead of it in cases of aspirin allergy.

Thienopyridines* (*clopidogrel* and *prasugrel*)** are irreversible $P2Y_{12}$ receptor blockers. ***Ticagrelor is a cyclopentyltriazolopyrimidine reversible $P2Y_{12}$ receptor blocker. ***Cangrelor,*** is an IV, fast-acting, $P2Y_{12}$ inhibitor. There is no antidote for P2Y12 inhibitors. Clopidogrel and prasugrel are "prodrugs" that require activation in the liver via the cytochrome P450 system. Ticagrelor is not a pro-drug, but requires twice-daily dosing owing to its short half-life.

No antidotes have been so far available for $P2Y_{12}$ receptor blockers. Platelet transfusion and desmopressin are recommended in cases of active bleeding.[16] Bentracimab, a monoclonal antibody fragment has been shown to reverse ticagrelor in a dose-dependent manner within 5 min from the initiation of the infusion. Non-fatal thrombotic events occur in 5% of patients.[16, 17]

Clopidogrel (loading dose 300-600 mg po followed by 75 mg/day, starting on presentation) is recommended for up to one year (CURE trial).[18] There is a high degree of clopidogrel response variability related to genetic and non-genetic factors. Binding of metabolized clopidogrel to platelet adenosine diphosphate (ADP) receptors on the platelet surface is catalysed 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.[19 20] However, among patients with acute coronary syndromes or atrial fibrillation, the effect of clopidogrel as compared with placebo has been found consistent, irrespective of CYP2C19 loss-of-function carrier status.[21] Other genetic variations such as the ABCB1 3435 TT genotype may also affect the pharmacokinetics, and clinical efficacy of clopidogrel.[21] Platelet function assays employ several methods for monitoring platelet reactivity.[22] Randomized trials have produced inconclusive results for a guided therapy by means of platelet aggregation monitoring or genetic testing [23-25] but recent clinical trials and meta-analyses have demonstrated that a precision medicine approach in which loss-of-function carriers are prescribed ticagrelor or prasugrel and noncarriers are prescribed clopidogrel results in reducing ischemic events without increasing bleeding risk.[26, 27] Thus, *CYP2C19* genetic testing before prescription of clopidogrel or ticagrelor/prasugrel in patients with ACS or PCI can be beneficial.[27] Clopidogrel maintenance (150 mg) doses has not improved outcome in patients with higher residual platelet reactivity that defined poor response.[28, 29] Ticagrelor is probably the alternatives in high-risk patients with poor response (ie patients with stent

thrombosis while taking clopidogrel), since insufficient platelet inhibition may also occur with prasugrel.[30] In stable patients, prasugrel and ticagrelor exert similar levels of P2Y12 inhibition. Clopidogrel is preferable to ticagrelor and prasugrel for patients over 70 years old (and especially >-80 years) and at high risk of bleeding.[31, 32]

Omeprazole and esomeprazole are proton-pump inhibitors that also inhibit the cytochrome enzyme CYP (high affinity for CYP2C19 and moderate affinity for CYP3A4), and the FDA has required label cautions in 2009 and 2011, respectively. Pantoprazole that inhibits the enzyme less than omeprazole should lessen the risk when taken 4 h after clopidogrel.[33] However, randomized clinical trials have produced inconsistent results. A meta-analysis of the studies assessing PPIs as a class, consistently reported higher 1-year event rates in patients receiving the drugs, while data from RCTs evaluating omeprazole vs placebo showed no difference in ischemic outcomes.[34] Thus the combination of clopidogrel with a proton-pump inhibitor should not be avoided in patients who are at increased risk of gastrointestinal bleeding.[35] PPIs may potentiate VKA-induced anticoagulation, resulting in increased INR values and bleeding risk, most likely due to facilitated gastric absorption of warfarin; thus careful monitoring is required.[36] Proton-pump inhibitors may be associated with increased risk for adverse cardiovascular outcomes following myocardial infarction, regardless of clopidogrel use,[37] and interference with the clearance of asymmetrical dimethylarginine (ADMA), the endogenous antagonist of nitric oxide synthase, has been reported.[38] However, in a PLATO substudy, a similar association was observed between cardiovascular events and PPI use during ticagrelor treatment as with clopidogrel treatment. This suggests that PPI use may be a marker for, than a cause of, higher rates of cardiovascular events in sicker patients who need a PPI.[39] They should be used in patients at an increased risk of gastrointestinal bleeding.[40]

A diminished pharmacodynamics response to clopidogrel has also been observed when coadministered with lipophilic statins and calcium channel blockers, but in clinical practice no increased cardiovascular risk has been demonstrated with these combinations.[41-43] Clopidogrel metabolites can inhibit enzymatic activity of cytochrome P4502C9 and lead to increased plasma levels of NSAIDS.

Clopidogrel hypersensitivity is manifested as generalized exanthema 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.[44] Allergenic cross-reactivity with ticlopidine, prasugrel, or both is present in a significant number of patients with clopidogrel hypersensitivity. Detailed recommendations for antithrombotic therapy in the elderly have been provided.[45]

Although clopidogrel should be ideally stopped 5 days before CABG, but, if needed, CABG can be performed in patients on clopidogrel.[46]

Switching from clopidogrel is achieved by a loading dose of 60 mg of prasugrel followed by 10 mg od 24 h later, or a loading dose of 180 mg of ticagrelor followed by 90 mg bd 12h later.[47, 48]

Ticagrelor (loading dose 180 mg po, 90 mg twice daily) is a reversibly binding P2Y12 inhibitor with a plasma half-life of <12 h. It is an active drug (clopidogrel and prasugrel are pro-active drugs), and beyond its antiplatelet efficacy, may exert cardioprotective effects via adenosine-dependent mechanisms, [49] and potential antibacterial activity has been reported.[50] It has been shown to reduce mortality and stent thrombosis in ACS compared to clopidogrel regardless of revascularization (PLATO trial).[51, 52] Total major bleeding rates were similar, but non-procedure-related major bleeding was increased with ticagrelor. [53] In a substudy of the PLATO trial, elevated hs-TnT predicted substantial benefit of ticagrelor over clopidogrel both in invasively and noninvasively managed patients, but no apparent benefit was seen at normal hs-TnT.[54] In a network meta-analysis, as compared to clopidogrel, only ticagrelor was associated with greater cardiovascular mortality reduction, while both ticagrelor and prasugrel were associated with a higher bleeding risk.[55, 56] 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 with clopidogrel. Patients with acute coronary syndrome with a prior history of ischemic stroke or TIA have higher rates of adverse cardiac events and stroke, and ticagrelor is probably preferable to clopidogrel.[57] In the elderly (>=80 years) clopidogrel appears to be safer than ticagrelor.[32] Of note, in stable patients subjective to elective PCI, ticagrelor is not superior to clopidogrel (ALPEUS trial).[58] In patients with diabetes, ticagrelor exerts similar or greater inhibition of ADP-induced platelet reactivity in comparison with prasugrel.[59]

Ticagrelor increases 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 and AV node suppression, and mild dyspnea without any adverse effect on cardiac or pulmonary function may be seen and are believed to be adenosine-mediated, although an inhibitory effect on the central nervous system is also possible.[60, 61] Higher adenosine levels induced by inhibiting adenosine uptake by red blood cells probably contribute to its efficacy.[62] Dyspneoa may lead to ticagrelor discontinuation,[63] but a reduced dose of lower dosing (60 mg bd) results in lower dyspneoa rates without compromising the degree of P2Y12 inhibition.[64] A lack of efficacy among US patients that was initially reported, and a probable reduced effect in coadministration with high dose aspirin (325 mg as

opposed to 75 mg, attributed to increased vascular resistance through inhibition of cyclooxygenase within blood vessels) are not matters of concern.[65]

Switching from ticagrelor to clopidogrel one month after ACS is superior to an unchanged DAPT strategy to prevent bleeding complications without increasing ischaemic events in stable patients.[66] A loading dose of 600 mg of clopidogrel, 12-24 h after ticagrelor discontinuation, is necessary to mitigate an increase in platelet reactivity, except in patients switching therapy because of bleeding.[67]

Prasugrel (60 mg loading dose, then 10 mg od) is more consistent than clopidogrel, with faster onset of action and fewer potential drug interactions. It has been shown to be better than clopidogrel in patients with NSTEACS particularly in those with diabetes for reducing adverse cardiac events and late stent thrombosis, but to increase major bleeding (TRITON-TIMI 38 trial).[68] Ticagrelor and prasugrel compared to clopidogrel, reduce major adverse cardiac effects, cause less stent thrombosis and decrease mortality without increased risk of bleeding following PCI in STEMI patients.[69] Ticagrelor and prasugrel appear to be similarly effective in this respect,[70, 71] although an increase in recurrent myocardial infarctions had been detected with ticagrelor.[72] 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). It has been found superior to ticagrelor in patients with acute coronary syndromes and for whom invasive evaluation was planned (ISAR-REACT 5 trial).[73] However, in a subsequent Swedish registry-based, cluster-randomized trial in an unselected population of patients with an acute coronary syndrome who had undergone PCI, the risk of ischemic events was not lower with a default prasugrel policy than with a default ticagrelor policy.[74] In patients who do not undergo revascularization, prasugrel does not significantly reduce mortality and myocardial infarction, as compared with clopidogrel (TRILOGY ACS).[75] In the ACCOAST trial on patients with NSTE myocardial infarction who were scheduled to undergo catheterization within 48 hours after admission, pretreatment with prasugrel at the time of diagnosis did not reduce the rate of major ischemic events up to day 30 but increased the rate of major bleeding complications.[76] In the PREMIUM RCT, among patients with STEMI who were undergoing primary PCI, low-dose prasugrel monotherapy initiated before PCI was not noninferior to DAPT for 12 months with respect to a composite of death from any cause, stroke, or myocardial infarction at 12 months.[77]

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. An 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.[78] However, in the TRILOGY ACS trial the frequency of neoplasm detection was similar with prasugrel and clopidogrel.[79] 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 patient has a weight <60 kg. It is not recommended in patients >75 years or if the risk of CABG is high,[45] and is contraindicated in patients with a history of TIA/stroke. De-escalation of therapy with conversion to clopidogrel after the first week,[80] or the first month of treatment,[66] is also an option. Prasugrel should not be administered routinely to patients with UA/NSTEMI before angiography, such as in an emergency department, or used in patients with UA/NSTEMI who have not undergone PCI.

In patients in whom angiography is possible, pretreatment with a high-dose $P2Y_{12}$ has been questioned before demonstration of significant coronary disease needing intervention,[81, 82] but this notion is controversial.[83] Pretreatment with prasugrel before angiography in patients scheduled for PCI within the next 48h is avoided; the drug may be given only immediately before indicated intervention.[76] In primary PCI, low-dose prasugrel monotherapy initiated before PCI has been found not noninferior to DAPT for 12 months with respect to a composite of death from any cause, stroke, or myocardial infarction at 12 months (PREMIUM RCT).[84]

Cangrelor is an IV, fast-acting, $P2Y_{12}$ inhibitor (30 μg/kg bolus followed by an infusion of 4 μg/kg for at least 2h). In a pooled analysis in ACS, it has reduced PCI periprocedural thrombotic complications at the expense of increased bleeding.[85] Its fast action makes it attractive in the absence of pretreatment. In patients with ST-segment–elevation MI given oral ticagrelor, cangrelor administered at the time of primary percutaneous coronary intervention did not reduce acute MI size or prevent microvascular obstruction (PITRI RCT).[86]

Selatogrel, a $P2Y_{12}$ inhibitor is rapidly absorbed following single-dose subcutaneous injection (8 and 16 mg), and results in strong inhibition of platelet reactivity as early as 15 min that is maintained for ≥8 h and reversible within 24 h.[87] It is promising since it could be self-administered subcutaneously.

Cilostazol is a selective inhibitor of 3-type phosphodiesterase, is commonly used in east Asia as an antiplatelet agent, but outside of peripheral arterial disease, has not found wider acceptance in Western populations. It is an effective medical therapy for treatment of leg symptoms and walking impairment due to claudication but side effects include headache, diarrhea, dizziness, and palpitations that result in discontinuation of the drug by up to 20% of patients. [88]

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 high-risk percutaneous coronary intervention. The small-molecule inhibitors ***eptifibatide*** and ***tirofiban*** are short-acting and much cheaper with similar efficacy.[89] They require dose adjustment in in patients with poor renal function. Initial studies in ACS have indicated a reduction in mortality with their use. However, most have been conducted without the use of clopidogrel or new $P2Y_{12}$ receptor blockers. IIb/IIa inhibitors may be indicated in primary PCI and there has been evidence that intracoronary bolus administration results in improved myocardial perfusion compared to IV (INFUSE-AMI and CICERO trials),[90, 91] although this is not a consistent finding (AIDA-STEMI trial).[92] The benefits of GP IIb/IIIa inhibition are in high risk patients with large thrombus present on coronary angiogram. In elderly patients lower efficacy and higher rates of bleeding are seen.

IIb/IIIa inhibitors should be given with caution if urgent CABG is anticipated. Reversibility of action is slow with abciximab (48h to 1 week), and faster with tirofiban (4-8 h) and eptifibatide (2-4 h). Abciximab is cleared via the reticuloendothelial system, and no current recommendations exist for dose adjustment for patients with CKD.

Anticoagulants

Heparins

A low molecular weight heparin (such as enoxaparin) or unfractionated heparin is given as soon as possible. Pre-treatment with loading-dose UFH at first medical contact is associated with an improvement of spontaneous reperfusion of IRA without increasing the risk of major bleeding.[93, 94]

Unfractionated heparin (UFH) is a heterogeneous group of negatively charged, sulfated glycosaminoglycans (molecular weight 3000 to 30 000 Da) from animal sources. UFH activates antithrombin through the formation of a heparin-antithrombin complex that inhibits other coagulation factors.[95] UFH inhibits both factor Xa and thrombin equally. 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 requirement for monitoring of aPTT. Elimination of the drug is mainly by the reticuloendothelial system and secondary by the kidneys.[96] The anticoagulant response to heparin is nonlinear at therapeutic doses, with a biological half-life of heparin increasing from ≈30 minutes after an IV bolus of 25 U/kg to 60 minutes with an IV bolus of 100 U/kg.[97]

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

Low molecular weight heparins (LMWH) (*enoxaparin*, *dalteparin, fraxiparin*) are specific inhibitors of factor Xa and, to a lower extend, thrombin with high bioavailability. Low-molecular-weight heparins (LMWH; molecular weight, 2000 to 10 000 Da) are produced

from unfractionated heparin by chemical or enzymatic processes. They can be given subcutaneously and provide more consistent anticoagulation avoiding the need for monitoring. LMWH are associated with a lower risk for heparin-induced thrombocytopenia than unfractionated heparin. Half-life is 3-4 h. Disadvantages are the partial only reversibility by protamine, renal excretion, and reduced efficacy against the contact activation pathway (factor XII) that contributes to thrombosis on catheter tips, stents, and filters (Figures 8 and 9).[95] No much data exist about other LMWH but they might be used if enoxaparin is not available. Enoxaparin reduces death and myocardial infarction compared to unfractionated heparin in NSTEACS.[98] If PCI is indicated, no additional dose is needed if the last SC dose was given <8h. If CABG is planned, LMWH should be discontinued 12-24 h before and replaced with UFH. LMWH are eliminated by the kidney (up to 80%) and are not recommended in patients with creatinine clearance <30 mL/min or in haemodialysis patients. Enoxaparin may be discontinued after PCI in stable, uncomplicated cases.

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 in patients at high risk of heparin-induced thrombocytopenia. In moderate- and high-risk patients, bivalirudin alone has similar ischaemic benefit as either unfractionated heparin or enoxaparin with a IIb/IIIa antagonist but with a reduction in major bleeding (ACUITY, ISAR-REACT 4, and BRIGHT-4 RCTs).[99-101] However, its superiority over heparin has been questioned by several negative trials, especially regarding patients with ST-elevation MI for whom acute stent thrombosis rates were increased with bivalirudin.[102-105] Meta-analyses have shown that bivalirudin increases the risk of myocardial infarction and stent thrombosis compared to heparin in patients subjected to PCI,[106 107] but this has been refuted in a meta-analysis on patients with ACS but without ST-elevation MI.[108]

Dabigatran (an oral direct thrombin inhibitor), has not been successful due to increased bleeding risk without reducing ischemic events (RE-DEEM trial).[109]

Direct factor Xa inhibitors

Fondaparinux reduces major bleeding and improves clinical outcomes compared to enoxaparin with or without a IIb/IIIa (OASIS-5).[110] In patients managed conservatively it is preferred over LMWH, especially when there is high risk of bleeding.[111] If these patients proceed to coronary intervention, a single bolus of UFH (85 IU/kg adapted to ACT, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors), should be given. Fondaparinux has been found to reduce 30-day death or myocardial infarction compared to unfractionated heparin, regardless of administration of fibrinolysis (OASIS-6).[112] 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 were observed in OASIS-5 with fondaparinux when compared with enoxaparin, even in patients with severe renal failure. Fondaparinux should be stopped 24 h before CABG and replaced by UFH. It is not recommended when an invasive approach is planned because catheters are prothrombotic due to their propensity to activate factor XII, thereby initiating the contact pathway of coagulation. Heparin and, to a lesser degree attenuate this phenomenon but fondaparinux is unable to inhibit catheter-induced clotting.[113]

Rivaroxaban (an oral Xa inhibitor) has been used post-discharge. It was shown to reduce the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke in patients with a recent acute coronary syndrome, when added to standard antiplatelet therapy (2.5-5 mg bd), but at an increased risk of major bleeding and intracranial hemorrhage (ATLAS 2 trial).[114] The 2.5 mg bd dose also reduced cardiovascular mortality at an increased risk of bleeding which was less than that of the higher dose, but overall resulted in a net reduction in fatal or irreversible events.[115] In the GEMINI-ACS-1 trial, combining low-dose rivaroxaban (2.5 mg bd) with a P2Y12 inhibitor for acute coronary syndromes had similar risk of clinically significant bleeding as aspirin and a P2Y12 inhibitor.[116]

Apixaban (oral Xa inhibitor), has been tried in doses similar to those used in AF (5 mg bd) in addition to standard antiplatelet therapy, but did not reduce ischemic events (APPRAISE 2 trial).[117] Apixaban was also associated with increased major bleeding, including intracranial hemorrhage.

In a meta-analysis, addition of a novel anticoagulant to dual antiplatelet therapy reduced cardiovascular events by 13%, but more than doubled the bleeding.[118]

Patients on Warfarin or Direct Oral Anticoagulants

Coronary angiography or PCI can be performed in patients on oral anticoagulation (warfarin or direct oral anticoagulants-DOAC) and with additional anticoagulation (UFH, LMWH), preferably through a radial access.[119] In patients at high risk of bleeding, oral anticoagulation may have to be temporarily stopped.[120] Oral anticoagulation is a relative contraindication for fibrinolysis. If, however, it is deemed clinically necessary, additional UFH or enoxaparin should be avoided until the INR is <2 or the NOAC effect has decreased (12 h or longer after last intake).[121]

Warfarin use alone increases the risk of bleeding to 13% per year, and the combination with an antiplatelet agent may triple this risk.[122] The incidence of fatal or non-fatal bleeding per 100 person-years of therapy has been found 14.2 for triple therapy, 7-10.6 for dual therapy, and 6.6-7 for monotherapy.[123] The risk of gastrointestinal bleeding with triple therapy is higher in elderly (>60 years) patients.[124] PPIs may potentiate VKA-induced

anticoagulation, resulting in increased INR values and bleeding risk, most likely due to facilitated gastric absorption of warfarin; thus careful monitoring is required.

Long-term triple therapy with an anticoagulant (warfarin or DOAC), aspirin, and clopidogrel, avoiding ticagrelor or prasugrel, may be necessary but at an increased risk of bleeding.[125, 126] However, there is the possibility of an increased risk of MI during the first month of therapy, thus prompting the recommendation for triple therapy during the first 1-4 weeks (Figure 4).[127] The bleeding risk with triple therapy is higher in patients >90 years of age or with a CHA_2DS_2-VASc score >6 or with a history of a major bleeding.[128] Preferred INR with triple therapy is 2-3, and 2-2.5 in the elderly and those at increased risk of bleeding.[123]

The optimum duration of triple therapy after stenting may differ on the basis of individual patient characteristics (and especially HAS-BLED score), stent, and drug characteristics.[129] In patients undergoing PCI, a DOAC is preferred over warfarin when oral anticoagulation is needed. [130, 131] Reduced dose rivaroxaban, 15 mg od, or 10 mg od with creatinine clearances 30-50 ml/min, (PIONEER AF-PCI) with clopidogrel without aspirin,[132, 133] or full-dose dabigatran (RE-DUAL PCI),[134] or apixaban (AUGUSTUS trial)[135] or edoxaban (ENTRUST-AF PCI)[136] with a $P2Y_{12}$ without aspirin, are also safer by means of bleeding without reducing efficacy than triple therapy with a DOAC, aspirin and a $P2Y_{12}$. In a further analysis of the AUGUSTS trial, aspirin acutely and for up to 30 days resulted in an equal trade-off between an increase in severe bleeding and reduction in severe ischemic events. After 30 days, aspirin continued to increase bleeding without significantly reducing ischemic events.[137]

Specific recommendations are also provided in Table 7, and Figures 5 and 6. For recommendations in patients with a prosthetic heart valve see the relevant Chapter.

Other Medications

Lipid Management

Higher risk among patients with ACS supports more aggressive LDL-C targets in patients with recent ACS compared with those with chronic CAD.[138] A detailed discussion can be found in the Chapter on Prevention. Specific recommendations for ACS are provided in Table 8 and Figure 7.

ACE inhibitors (or Angiotensin Receptor Blockers)

Should be administered orally within the first 24 h to patients with pulmonary congestion or LVEF<= 0.40, in the absence of hypotension (systolic blood pressure < 100 mm Hg or < 30 mm Hg below baseline) or other contraindications (Table 9). They may also be used in all patients provided the systolic blood pressure is >100 mm Hg.

Beta-blockers

Patients on chronic β-blocker therapy admitted with ACS should be continued on ß-blocker therapy if not in Killip class ≥III. They should also be started after STEMI , and, most probably, even in the absence of LV dysfunction (Table 9). In patients with mild to moderate asthma (not in the acute phase) cardioselective beta blockers may also be used in minimum doses.[139] IV β-blockers are useful in patients developing fast AF in the absence of heart failure.

Calcium channel blockers

In the presence of recurrent symptoms or Prinzmetal variant angina or in patients in whom beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., *verapamil* or *diltiazem*) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications. Dihydropyridines are contraindicated in the absence of a beta blocker.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, NSAIDs except for ASA, whether nonselective or COX-2 selective agents, should be discontinued at the time a patient presents with ACS. Following MI NSAIDs (both non-selective and selective COX-2 inhibitors) are associated with a 45% increase of risk of recurrent MI or death even with only one week of treatment. Diclofenac confers the highest risk, whereas naproxen is probably the safest agent (see also Chapter on Stable CAD). [140]

Randomized trials have been controversial, but therapy with ***aldosterone antagonists*** in patients with STEMI but without heart failure or with a LVEF>40% may be beneficial.[141]

Lidocaine infusion to supress ventricular ectopy is no more indicated.

IV ***magnesium*** routinely is not indicated unless if a deficit is documented.

Despite initially promising results, the use of ***colchicine*** is not established (See Specific Therapy of STEMI).

Recommendations for the in-hospital management of patients with ACS are presented in Table 10.

Non-ST-Elevation Myocardial Infarction: Specific Therapy

Criteria for an invasive strategy are presented in Tables 11 and Figure 8, and Table 12, and Figures 9 and 10. Thus, current guidelines suggest that in high-risk, unstable patients, intervention within 12-72 hours is preferred while either an early or a delayed approach may be adopted in other patients. Revascularization in this setting mainly employs percutaneous coronary intervention (PCI) of the culprit and additional lesions. Several trials and meta-

analyses have established the superiority of intervention over medical therapy in high-risk patients.[142-158] In addition, a five-year follow-up of patients with non–ST-elevation acute coronary syndrome from FRISC II, ICTUS, and RITA-3 Trials 3 trials showed no association between a procedure-related MI and long-term cardiovascular mortality, although there was a substantial increase in long-term mortality after a spontaneous MI.[159]

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, depends on the patient's condition and risk factors (Figure 9).[160-163] Early intervention seems to be beneficial in high-risk patients as shown in the TIMACS[145] and a meta-analysis where an early invasive strategy (<14h) reduced mortality in high-risk patients such as those with elevated biomarkers, a GRACE risk score>140, diabetes, or age>75 years.[162] The beneficial effect of an early invasive strategy in patients with a GRACE score>140 were also verified in the subsequent VERDICT trial.[156] Early angiography (<14 h) with a view to PCI has been found superior to a strategy of preceding anticoagulation and subsequent intervention in patients with NSTE-ACS. [162] by reducing residual ischemia and the duration of hospital stay and may also reduce complications, such as bleeding, and major events (death, MI, or stroke). [142, 145, 161 163] Patients with ACS and acute heart failure are always considered a very high-risk group, and an immediate invasive strategy is also recommended in these patients, regardless of ECG or biomarker findings.[164] However, in a meta-analysis of 17 RCTs, early intervention did not reduce all-cause mortality, MI, admission for HF, repeat revascularization, or increase major bleeding or stroke when compared with a delayed intervention.[165] No benefit with a routine invasive approach has been also seen in post-CABG patients with NSTE-ACS.[166] Thus, the decision should be taken on an individual basis.

Other risk stratification models are also useful for subsequent decision making. The extent of coronary artery disease is important. The Syntax Score is an independent predictor of the 1-year rates of death, cardiac death, MI, and target vessel revascularization, in patients undergoing PCI, with a score >8 indicating increased mortality.[167 168] Patients who demonstrate a totally occluded culprit vessel on coronary angiography are at higher risk of mortality and major adverse cardiac events.[169] In older adults (mean age 82 years and 32% of them frail), with NSTEMI, an invasive strategy did not result in a significantly lower risk of cardiovascular death or nonfatal myocardial infarction (the composite primary outcome) than a conservative strategy over a median follow-up of 4.1 years (SENIOR-RITA RCT).[170]

Revascularization Strategies

Incomplete revascularization after PCI in ACS, defined as additional stenoses with a diameter percent stenosis 30-70%,[171] or a residual Syntax Score >8.0, [172] is associated with a poor prognosis, and a single-session complete revascularization is probably preferable.[173, 174]

However, in the FULL REVASC RCT, among patients with STEMI or very-high-risk NSTEMI and multivessel coronary artery disease, FFR-guided complete revascularization was not shown to result in a lower risk of a composite of death from any cause, myocardial infarction, or unplanned revascularization than culprit-lesion-only PCI at 4.8 years.[175] A radial approach reduces bleeding complications and all-cause mortality (MATRIX trial).[176, 177] Culprit lesion ambiguity can be present in more than 30% of patients with suspected NSTE-ACS and over 10% of patients may have multiple culprit lesions.[178] Intravascular imaging is useful in ACS patients without significant obstructive CAD on coronary angiography. Diabetic patients with acute coronary syndrome and multivessel disease enrolled in the ACUITY trial, had less bleeding and acute kidney injury, greater need for repeat revascularization procedures, and comparable rates of myocardial infarction, stroke, and death through 1-year follow-up, when treated with PCI rather than CABG.[179]

A considerable number of patients with NSTEMI developed periprocedural myocardial injury with or without type 4a myocardial infarction after PCI. A post-PCI change in troponin I >40%, along with an absolute postprocedural value of ≥5 times the 99th percentile upper reference limit, appears to be the optimal threshold for defining prognostically relevant injury. These events are associated with a significantly increased risk of 1-year adverse outcomes and occurred more frequently than in patients with chronic coronary syndromes.[180]

Multivessel Disease

The management of patients with multi-vessel disease is presented in Table 13 and Figure 11. In an analysis of the CARE Registry data, no clear evidence of a clinical benefit for either PCI or CABG was determined in well-matched patients who were adherent to recommended medical therapy.[181] In patients in whom CABG is indicated after angiography aspirin and UF heparin are continued. Ticagrelor and clopidogrel should be ideally stopped 5 days and prasugrel 7 days before CABG if this is possible.[182] However, in the SWEDHEART Registry discontinuation of ticagrelor 3 days before surgery did not increase the incidence of major bleeding, as happened with clopidogrel, probably due to faster off-set of action of ticagrelor.[183]CABG within 24 hours of non–ST-segment–elevation MI has been associated with in-hospital mortality and long-term outcomes similar to those of CABG performed after 3 days, despite dual antiplatelet therapy.[184] Enoxaparin should be stopped 12-24 h, fondaparinux 24 h, and bivalirudin 3 h before the procedure, respectively, and replaced by UF heparin. IIb/IIIa (eptifibatide or tirofiban) are discontinued 4 h before surgery (abciximab requires much longer time, at least 48h). If the patient has already received a stent, cangrelor a selective P2Y12 inhibitor may be more effective as bridging therapy than heparin.[185]

Technical aspects of PCI in ACS are discussed in the STEMI section.

ST-Elevation Myocardial Infarction: Specific Therapy

Development of a regional system of MI care and participation in relevant programmes as outlined in current guidelines is essential for the optimal care of patients. Recommendations for selection of reperfusion method are provided in Table 14 and Figure 12, and Table 15 and Figure 13.

Primary PCI

Primary PCI is now the preferred mode of therapy and results in 25-30% lower mortality (7% vs 9%), less reinfarction (3% vs 7%), and stroke (1% vs 2%) than fibrinolysis.[186] Re-infarction incidence following stent implantation is 1.8% at 30 days and 4% at one year, mainly due to stent thrombosis (>75%).[187] Patients who survive the first 30 days after a STEMI treated with primary PCI have an excellent prognosis, with a <1.5% annual risk of successive cardiac death during the next 5 years.[188] The benefit of PCI over fibrinolysis increases with greater delay in presentation, particularly after 120 min of symptom onset, and in patients >65 years of age, but is lost with a relative delay (door-to-balloon time vs door-to-needle time) of more than 114 min.[189-191] Each 30-min delay in reperfusion results in a 7.5% increase in 1-year mortality. Delays in door-to-balloon time for PCI greater than 1 h over when thrombolytic reperfusion would have occurred, may negate the mortality benefit of PCI. The greater the baseline patient risk, and the availability of in-hospital PCI facilities, the longer the acceptable primary PCI delays.[192] Ideally, the door to needle time should be <=90 min, or <=120 min after the first medical contact. In a report of the CathPCI Registry, as well in other previous studies, reduction to 67 min did not translate into reduced in-hospital mortality,[193] but this has been attributed to patient and procedural factors.[194]

Primary PCI has been generally recommended for up to 24 h after the onset of symptoms, but in some patients the true onset may be difficult to determine. This time limit may be extended to 24-48 h in the presence of ongoing ischemia, or even in stable patients.[195, 196] The ESC guidelines on acute coronary syndromes consider revascularization in asymptomatic patients presenting between 12 and 48 h after symptom onset,[178] mainly based on the results of the BRAVE-2 trial.[195] The latest ACC/AHA guidelines adopt a 24-h cut-off.[138] When the patients presents >24 hours after symptoms onset and with a definitely occluded infarct-related artery, the open artery trial (OAT) showed no benefit of PCI in stable patients and is not recommended by current guidelines,[197] although ventricular remodelling is affected by the presence of a patent artery, and LAD reopening might possibly be beneficial.[198] LV function at presentation is a strong predictor of short- and long-term mortality following primary PCI.[199] PCI is also the treatment of choice in cardiogenic shock. The presence of significant stenosis or total occlusions in non-MI related arteries indicates

adverse prognosis.[200] It should be also noted that MI with RBBB is frequently caused by the complete occlusion of the infarct-related artery and in-hospital mortality is highest from all ECG presentations of AMI. Thus, RBBB should be considered as a standard indication for reperfusion therapy, in the same way as LBBB.[201]

PCI is preferred over fibrinolysis if:

1. Presentation <12h (and ideally <2h) after onset of symptoms, or even <24h, especially in the presence of ongoing ischaemia.
2. Can be performed with a delay < 120 minutes of first medical contact-to-balloon time.
3. Cardiogenic shock, or severe heart failure.
4. Contraindications to fibrinolysis or diagnosis of STEMI in doubt.

A reasonable policy in places without immediate PCI facilities is to fibrinolyse all patients who present within 12 hours from onset of symptoms, using half-dose for patients >=75 years of age, and then perform angiography and PCI if indicated 2-24 hours later.[202-205]

No-reflow phenomenon

Persistent no-reflow is linked to higher complication rates and mortality. Its incidence varies widely [from ∼3% in stable elective percutaneous coronary intervention (PCI) to as high as 40%–60% in high-risk settings] and is more frequent during PCI for ST-elevation MI (STEMI) and degenerated saphenous vein grafts (SVG) and after rotational atherectomy.[206] No reflow is assessed by resolution of ST-segment elevation or contrast flow by angiography (Table 16). Microvascular function after STEMI is also assessed by indices such as the angiographic tissue myocardial perfusion grade, and the index of microvascular resistance.[207] Coronary embolization and ischemia-induced endothelial swelling and neutrophil and platelet activation are thought responsible. Adenosine as continuous infusion of 70 mcg/kg/min over 3 hours during and after PCI, or intracoronary bolus of 30–60 mg, verapamil as intracoronary bolus of 0.5–1 mg, and intracoronary nicardipine or nitroprusside may also be used.[208] A strategy of balloon angioplasty or aspiration with deferred stenting 4-16 h later has been proposed to reduce no-reflow following primary PCI,[209] but more recent trials argue against such a strategy.[210, 211] Routine use of high-dose intracoronary adenosine and sodium nitroprusside during primary PCI did not reduce infarct size or microvascular obstruction.[212] High-dose intravenous N-acetylcysteine administered with low-dose intravenous nitroglycerin has been shown to reduce infarct size in patients with ST-segment-elevation myocardial infarction undergoing PCI, but without any effect on LV remodelling or LVEF at 3 months.[213] Sonothrombolysis with ultrasonic cavitation of intravenously administered microbubbles has been shown to result early epicardial patency, reduce infarct size, and improve systolic function in patients with STEMI undergoing primary PCI.[214] Intracoronary administration of

alteplase has not been found beneficial in patients undergoing primary PCI for STEMI and large thrombus burden.[215]

Thrombus aspiration

Thrombus aspiration had been found beneficial,[216-218] but its value has been questioned in recent trials,[91, 219-223] and there has been evidence that manual thrombus aspiration may increase the risk of stroke.[223-225] Embolic protection is not beneficial in reducing mortality compared with PCI alone, whereas mechanical thrombectomy appears to increase mortality.[226] Routine thrombectomy is not recommended in STEMI any more (ACC/AHA/SCAI 2021 GL on revascularization, III A - No benefit). See also the Chapter on Revascularization.

Complete revascularization

Non-culprit coronary interventions at time of primary PCI should be considered (Table 17 and Figure 11). Despite negative findings by previous observational studies, in all randomized trials (CvLPRIT, PRAMI, Compare-Acute, DANAMI-3-PRIMULTI, COMPLETE) preventive PCI in noninfarct coronary arteries with >70% diameter stenosis or with 50-69% stenosis and FFR<=0.80 following primary PCI, either simultaneously or before discharge, significantly reduced a composite endpoint of cardiac death, MI, or revascularization, compared with angioplasty limited to the infarct artery,[227-232] although it could lead to a small increase of CMR-detected, non-infarct related artery myocardial infarction.[233] In all relevant meta-analyses, multivessel revascularization either at time of primary PCI or as a staged procedure at the same or another hospitalization in patients with STEMI was associated with better outcomes.[177, 234, 235] Immediate or staged multivessel PCI provide similar results.[236, 237] Although in an analysis of the CathPCI Registry no benefit of multivessel revascularization was seen in the elderly (>65 years old),[238] in the FIRE RCT, physiology-guided complete revascularization resulted in a lower risk of a composite of death, myocardial infarction, stroke, or ischemia-driven revascularization at 1 year compared to culprit lesion only PCI.[239] in a subsequent individual patient data meta-analysis patients >=75 years of age with ST-segment–elevation myocardial infarction and multivessel disease, complete revascularization reduced the primary end point of death, myocardial infarction, or ischemia-driven revascularization up to 4 years. Of note, an FFR-guided strategy did not have a significant benefit over an angiography-guided strategy with respect to the risk of death, myocardial infarction, or urgent revascularization at 1 year, in patients with STEMI undergoing complete revascularization (at least one nonculprit major epicardial coronary artery or major side branch measuring ≥2.0 mm in diameter, with at least one lesion with stenosis of 50% or more in diameter (by visual assessment).[240] FFR-guided complete revascularization has not been shown superior to culprit lesion PCI.[175] However, in the AIR-STEMI RCT on patients with multivessel disease, a strategy of complete coronary-artery revascularization guided

by FFR resulted in a lower risk of a primary-outcome event (death, myocardial infarction, cerebrovascular accident, or ischemia-driven revascularization) than a strategy guided by conventional angiography.[241]

However, in patients with STEMI, multivessel disease and ***cardiogenic shock***, complete revascularization may be harmful. [242-245]

Other issues

The *radial* is now the recommended approach (Table 18). New generation ***drug-eluting stents (DES)*** are superior to ***bare-metal stents (BMS)*** for primary PCI.[246, 247] ***Direct stenting*** can be safely performed.[222] The strategy of deferred stenting is not beneficial.[211] ***Clopidogrel reloading*** in patients already on clopidogrel is safe and probably beneficial.[248] Primary PCI can be performed in patients on ***oral anticoagulation*** (warfarin or NOAC) and with additional anticoagulation (UFH or LMWH), preferably through a radial access, that reduces bleeding complications.[176, 177, 249, 250] ***Lesion calcification*** indicates increased thrombotic complications and mortality.[251] Patients with spontaneous ***coronary dissection***, usually present with an acute coronary syndrome. Results of PCI are suboptimal and CABG may be needed. A conservative strategy is generally preferred, especially for dissection of small and medium-sized vessels with TIMI grade 2 or 3flow.

Pharmaco-invasive therapy

Initial studies on ***facilitated PCI*** ie full of half-dose thrombolysis with or without IIb/IIIa inhibitors followed by immediate PCI, documented an increased incidence of major adverse cardiac events. [252, 253] However, in the FAST-MI trial on patients presenting <=3h from symptoms onset, the 5-year survival was similar between primary PCI and fibrinolysis followed by coronary angiography and high rates of subsequent PCI at varying time intervals.[254] Most of the existing evidence indicates that routine PCI within 24 h but later than 2-3 hours after fibrinolysis is the optimal strategy and may offer reduced rates of reinfarction and composite outcomes of myocardial infarction and death compared to ischemia-guided PCI. [202-205] In the EARLY-MYO trial on patients presenting <=6h after symptom onset and for whom the expected PCI delay was >=60 min, half-dose alteplace followed by PCI 3 to 24h later (or in 90 min if there was a <50% resolution of ST-segment elevation) was superior than primary PCI performed 1 to 3 h later.[255] In the CAPTIM trial, patients treated within 2 h of symptom onset, had a lower 5-year mortality with pre-hospital fibrinolysis.[204] In the STREAM trial, prehospital fibrinolysis with tenecteplace in patients who presented within 3 hours after symptom onset and who were unable to undergo primary PCI within 1 hour (with half the dose in those >75 years), resulted in effective reperfusion compared to late primary PCI (6-24 h from symptom onset), but with a slightly increased risk of intracranial bleeding,[202] although one-year mortality was similar in the two groups.[256] In the TRANSER-AMI trial on high-risk patients who were treated with fibrinolysis, transfer for PCI within 6

hours after fibrinolysis was associated with significantly fewer ischemic complications than was standard treatment.[205] In the FAST-MI French registry, patients who had pPCI beyond the recommended 120 min period had poorer 5-year outcomes compared to those subjected to a pharmaco-invasive strategy.[257] If these timelines cannot be achieved, a pharmaco-invasive strategy should be instituted, as it may increase long-term survival and event-free survival, compared to a late primary PCI strategy, therefore, lending support to current guidelines. Thus, in patients presenting early after symptoms or when a timely PCI is not available, fibrinolysis followed by PCI at least 2 hours and up to 24 hours later, may be at least as good as primary PCI.[258, 259]

Fibrinolysis

Fibrinolysis is given ***within the next 12 h after the onset of symptoms or the next 24 h in case of ongoing ischemia*** (Tables 19 and 20). Patients presenting beyond the 12 h limit should receive heparin or fondaparinux regardless of whether reperfusion is attempted. Despite previous reservations, fibrinolysis recommended in the elderly (>75 years) when primary PCI is not available.[260, 261] Urgent pharmacological reperfusion with fibrinolysis, either prehospital within 30 min or after transfer with a door to needle time < 30 min, remains the principal treatment for improving survival after STEMI, unless an absolute contraindication exists. In patients presenting <2 hours after symptom-onset, fibrinolysis can achieve mortality rates of <4%, which are similar to those achieved by primary PCI. The earlier that fibrinolysis, the greater the benefit by means of preservation of left-ventricular function and reduction in mortality.[262]

Bolus-only fibrin-specific agents, ***rateplace (rPA),*** and ***tenecteplace (TNK-tPA***) are tissue plasminogen activator (tPA) mutants that achieve greater vessel patency than non-fibrin specific agents (streptokinase and urokinase). Both tenecteplace and rateplace confer decreased mortality compared to streptokinase as does ***accelerated infusion of alteplace*** but at a cost of increased bleeding compared to non-accelerated infusion.[263] Tenecteplace is the safest agent in this respect. In patients receiving fibrin-specific fibrinolytic agents, and perhaps streptokinase, ***unfractionated heparin*** or ***enoxaparin*** commenced early after fibrinolysis is recommended (Table 15). UFH should not be given for more than 48h due to the risk of heparin-induced thrombocytopenia. Maintenance dosing with enoxaparin or fondaparinux should be continued for the duration of the index hospitalization, up to 8 days.

Glycoprotein ***IIb/IIIa inhibitors*** increase the risk of major bleeding and should be avoided.[263] Combination of half-dose fibrinolytics and glycoprotein IIb/IIIa inhibition for pharmacological reperfusion achieves more rapid ST-segment resolution, and less recurrent infarction than with standard fibrinolytic therapy, but no reduction in mortality.[264] It is contraindicated in patients >75 years old.

Intracranial haemorrhage

The occurrence of a change in neurological status during or after reperfusion therapy, particularly within the first 24 hours after initiation of treatment, is considered to be due to intracranial haemorrhage until proven otherwise. The incidence of intracranial hemorrhage following thrombolysis has been estimated between 0.2 to 2%.[265] Certain patient groups such as the elderly, women, hypertensive patients and diabetics are at an increased risk of intracranial hemorrhage when subjected to thrombolysis. Fibrinolytic, antiplatelet, and anticoagulant therapies should be discontinued until brain imaging scan shows no evidence of intracranial haemorrhage. Cryoprecipitates, fresh frozen plasma, protamine, and platelets are given and intracranial pressure is reduced with mannitol, endotracheal intubation, and hyperventilation. Blood pressure and glucose levels are optimized and neurosurgical consultation is sought. For further discussion see also Chapter on AF.

Failed reperfusion

Criteria of successful thrombolysis are:

ST resolution (>70%) within the first 90 min after treatment

T wave invertion <4 hours after treatment

Rapid release of biochemical markers

Accelerated idioventricular rhythm 60-120 bpm (benign rhythm)

Failed reperfusion is defined as continuing chest-pain or failure of ST-segment resolution by more than 50% at 90 min after fibrinolysis and is seen in 40% of cases with fibrinolysis. Fibrinolytic therapy (other than streptokinase) may be repeated if PCI is not available within the next 60 min. Patients with ***recurrent ischemia*** should be considered candidates for coronary arteriography and PCI or CABG.

Rescue PCI

This is better than repeat fibrinolysis after failed reperfusion,[266] and associated with lower rates of heart failure (5% absolute reduction), and reinfarction (4% absolute reduction) by 6 months, but a 3% increase in stroke compared to a conservative strategy with PCI only for recurrent ischemia after fibrinolysis.[267] Coronary angiography with intent to perform PCI is also indicated in patients who received thrombolysis and develop cardiogenic shock, pulmonary oedema or CCF and hemodynamically compromising ventricular arrhythmias.

Routine angiography following fibrinolysis

ST recovery is an imperfect discriminator between TIMI grade 2 and TIMI grade 3 flow, with up to 50% of patients with persistent ST elevation having a patent infract-related artery at the time of angiography.[268] Thus, routine coronary angiography, and if indicated PCI, may be recommended in all patients after successful thrombolysis (Table 21). This should be done within the next 24 hours and delayed for at least 2 hours following the fibrinolysis, though the optimal timing remains uncertain.[269, 270] In stable patients who did not receive reperfusion, routine angiography before discharge is an option. See also Pharmaco-invasive therapy above.

CABG

CABG mortality is elevated for the first 3 to 7 days after infarction, and the benefit of revascularization must be balanced against this increased risk. However, emergency surgical revascularization may be necessary and can be undertaken especially in cases of failed PCI of a large LAD or mechanical complications of the MI.

Complications of ACS

The ESC recommendations for complications of ACS are summarized in Table 22.

Atrial fibrillation

The development of atrial fibrillation (approximately 2-21% of patients with ACS), carries a worse prognosis and predicts increased mortality, particularly when occurring >30 days after MI. [271-273] A history of AF in patients undergoing PCI is also associated with a worse outcome.[274] Haemodynamic instability due to high ventricular rates that do not respond to IV blockade may require DC cardioversion. For adaptation of anticoagulation in patients on warfarin or DOACs see the relevant section.

Ventricular Arrhythmias

Non-ST elevation acute coronary syndromes

Non-sustained VT is detected in 18-25% of patients 2 to 9 days after admission, and even short episodes of VT lasting 4 to 7 beats are independently associated with the risk of SCD over the subsequent year, especially when associated with myocardial ischemia.[275] Earlier episodes within 48 hours after admission do not carry the same risk. In the EARLY ACS trial, the cumulative incidence of sustained VT/VF is 1.5% with 60% of them occurring >48 h after enrollment.[276] Both early and late sustained VT/VF are associated with increased risk of death, even after adjustment for revascularization and LV function.[276] In the MERLIN-TIMI 36 trial, the presence of myocardial ischemia or VT alone as detected on 7-day continuous electrocardiographic monitoring, and particularly in combination, is independently associated with poor cardiovascular outcomes.[277] Appropriate revascularization as well as monitoring beyond 48h are indicated in this setting. Recommendations are provided in Table 26.

Acute myocardial infarction

VPBs with very short coupling intervals (<220 ms) interrupting the T wave of the preceding beat (R-on-T phenomenon) developing during an acute stage of myocardial infarction would predict the development of early cycled reentry, potentially culminating in VF.[278]

NSVT occurs in up to 75% of reperfused patients and during the first 13 [279] to 24 hours [280] does not carry a prognostic significance. In-hospital NSVT following this period indicates increased in-hospital mortality. However, in patients who had has a prior myocardial infarction treated with reperfusion and beta blockers, NSVT is not an independent predictor

of long-term mortality when other co-variates such as left ventricular ejection fraction are taken into account.[281] Following discharge after primary PCI, early ventricular arrhythmias are detected in 7% of patients.[282]

Accelerated idioventricular rhythm is a slow form of ventricular tachycardia (<100 bpm) which characteristically follows myocardial infarction. It tends to remain stable, usually does not give rise to ventricular fibrillation and does not require antiarrhythmic treatment. It is the most common arrhythmias during primary PCI (42%).[283]

Ventricular fibrillation during the acute phase (up to 48 h) indicates a higher in-hospital mortality, but survivors do not have adverse prognosis.[284]

Acute therapy

NSVT:

NSVT does not require antiarrhythmic drug therapy in the setting of an acute coronary syndrome. Electrolyte correction and oral beta blockers are useful.

VT:

Electrolyte correction.[285]

Beta-blocker therapy in the first 24 hours after STEMI is associated with decreased early mortality.[286]

IV amiodarone (5mg/kg bolus) may be used, but has been associated with increased mortality.[287]

Prophylactic lidocaine may also be used, but there are concerns about increased mortality. In a Cochrane review very little or no effect on mortality or ventricular fibrillation was documented, but the safety profile was unclear.[288]

Overdrive pacing may be also considered.

Unstable VT/VF refractory to cardioversion:

Intubation may be necessary in refractory VF/VT.

In haemodynamically unstable patients with recurrent VT or VF despite optimal therapy, an LVAD or extracorporeal life support should be considered.

Incessant VT or *electrical storm:*

IV beta blockers are especially indicated.[285, 289] The short-acting esmolol is preferred in the presence of reduced LV function with close monitoring due to the risk of cardiogenic shock.

Normalization of serum K (>4 mEg/L) and Mg (>2 mEq/L) is essential.

IV amiodarone (5mg/kg over 10 min, followed if necessary by repeat doses or constant infusion, total dose <2.2 g over 24 h), IV procainamide and perhaps lidocaine can be also considered.[285]

Urgent revascularization may be needed.

Cather ablation is now an option (see Chapter on VT).Specific recommendations are provided in Figure 14 and Tables 23 and 24.

Out of hospital cardiac arrest

The incidence of out of hospital cardiac arrest within 90 days after MI in the Swedish CPR Registry was 0.3%, with an initial shockable rhythm recorded in 36.4% of the patients.
In addition to LVEF, predictors of cardiac arrest are male sex, diabetes, renal impairment, heart failure, and newly identified atrial fibrillation or atrial flutter.[290] Acute coronary occlusions are present in 20% patients with out of hospital cardiac arrest without ST-segment elevation, irrespective of hemodynamic status. Acute coronary occlusions are typically associated with chest pain before cardiac arrest and an initial shockable rhythm.[291]
Recommendation are management are provided in Table 25.

Late ventricular arrhythmias

Late ventricular arrhythmias (>48h), particularly ***sustained VT*** are associated with long-term adverse outcome.[292] In patients discharged after primary PCI, early ventricular arrhythmias are detected in 7% of them.[282] Sustained monomorphic VT indicates pre-existing scar and does not respond to revascularization.

Atrioventricular Conduction Disturbances

The sinus node is supplied by the right coronary (60 %) or the left circumflex artery (40%). The atrioventricular node is supplied by the RCA (90%) or the left circumflex artery (10%). The bundle of His is supplied by the atrioventricular nodal branch of the RCA, and partially from the septal perforators of the LAD. The right bundle branch receives most of its blood from septal perforators of the left anterior descending artery and may be through collaterals from the RCA and Cx. The left anterior fascicle is supplied by septal perforators from the LAD and is particularly susceptible to ischemia or infarction. The left posterior fascicle is supplied by the RCA (through the AV nodal artery) and by septals of the LAD.[293] AV block in the post-MI period is a strong predictor of cardiac death.[294]

In the Global Registry of Acute Coronary Events, the incidence of high-grade AV block in acute coronary syndromes was low (2.9%) and decreasing, but it carried a high risk of in-hospital death (22.7%), reflecting the severity of ACS. [295] In the era of primary PCI, high-degree AV block is seen in 3.2% of patients with MI, usually inferior and more often in female patients >65 years of age, and indicates increased mortality.[296] **LBBB** does not suggest isolated LAD occlusion. In patients with LVEF<35%, **RBBB** has been associated with significantly greater scar size than LBBB and occlusion of a proximal LAD septal perforator causes RBBB.[297] In the Global Registry of Acute Coronary Events, the incidence of high-grade AB block in acute coronary syndromes was low (2.9%) and decreasing, but it carried a high risk of in-hospital death (22.7%), reflecting the severity of ACS. High-grade AV block

present at the time of presentation to hospital (vs. occurring in-hospital) and early (<12 h) percutaneous coronary intervention or fibrinolysis (vs.>12 h or no intervention) were associated with improved in-hospital survival, whereas temporary pacemaker insertion was not. [295]

Anerior MI. PR prolongation is often associated with a wide QRS complex (>0.12 second) with a right bundle-branch block pattern. Second-degree atrioventricular block with anterior myocardial infarction is usually Mobitz type II block secondary to block in the His–Purkinje system. Complete heart block may occur abruptly during the first 24 hours after myocardial infarction, and is almost always preceded by the development of right bundle-branch block with right or left-axis deviation and QR pattern in lead V1.

Inferior MI. Sinus bradycardia and various degrees of AV block (including complete) can occur within the first two hours due to increased parasympathetic tone, and resolve within 24 hours. Complete AV block complicating inferior MI is usually at the node level, ie with a narrow complex escape rhythm. A wide QRS escape rhythm suggests additional LAD disease.

Bradycardia during the first 24 hours responds to ***atropine***. After the first 24 hours symptomatic conduction disturbances require temporary pacing (Table 28). Prompt opening of the infarcted vessel is indicated in AV block, especially when due to inferior infarction, even in the case of late (>12 h) presentation.

There are no specific data on the optimal timing of ***permanent pacing*** post-STEMI, with or without fibrinolysis or primary PCI. The ESC GL on ACS recommend pacing if the block does not resolve within 5 days after the acute event. However, in inferior myocardial infarction, if the patient has narrow QRS and evidence of gradual improvement resolution of AV block may be seen after 1-2 weeks. Recommendations are provided in Tables 22 and 24.

Heart Failure

Most deaths in hospitalised patients with STEMI are due to heart failure and mechanical complications. The most commonly encountered mechanical complications are acute mitral regurgitation secondary to papillary muscle rupture, ventricular septal defect, pseudoaneurysm, and free wall rupture.[298]

Heart failure (Killip class II and III)

Oxygen by mask (4-5 lt/min), loop diuretics (ie frusemide 20-40 mg IV repeated at 1-4 hourly intervals), ACE inhibitors (or ARBs), and nitrates if the systolic BP>100 mm Hg are mandatory. Dobutamine (can be given through a peripheral line) or dopamine if there is hypotension (requires central line) can be considered in refractory cases.

Cardiogenic shock

Cardiogenic shock occurs in 5-8% of patients with ST-elevation myocardial infarction and 2.5% of non-STEMI.[299] Cardiogenic shock is caused by extensive loss of viable myocardial tissue and is characterized by: [300]

1) a sustained (>30 min) episode of systolic blood pressure <90 mm Hg;
2) cardiac index <2.2 l/min/m2 determined to be secondary to cardiac dysfunction; and/or
3) the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., intra-aortic balloon pump, extracorporeal circulation, or ventricular assist devices) to maintain blood pressure and cardiac index above those specified levels.

The CLIP predictive model including four blood-based biomarkers (lactate, interleukin-6, and NT-proBNP, and cystatin C,) has been found better that other scores (such as the IABP-SHOCK II) for risk stratification of patients with cardiogenic shock.[301]

Early revascularization by PCI or CABG reduces mortality that approaches 50% if left untreated (Table 26). [302] [245] However, despite major advances in PCI technique and antithrombotic therapy the last 20 years, the 30-day mortality still remained nearly unchanged in the range of 40–50%.[303] Observational studies on patients with STEMI and multivessel disease with cardiogenic shock, multivessel PCI was also associated with a significantly lower risk of all-cause death and non-infarct related artery repeat revascularization.[242, 243] However, in the CULPRIT-SHOCK RCT on patients in cardiogenic shock that complicates a STEMI, the 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower among those who initially underwent only PCI of the culprit lesion than among those who underwent immediate multivessel PCI.[245] Complete revascularization may be associated with harm and the issue is still debatable.[244] The effectiveness of intra-aortic balloon pumping is debated, particularly if revascularization is undertaken. [304-306] In the IABP-SHOCK II randomized trial intraaortic balloon counterpulsation did not significantly reduce mortality in patients with cardiogenic shock complicating acute myocardial infarction for whom an early revascularization strategy was planned.[306] Extracorporeal life support has also failed to reduce mortality.[307] Algorithms for the use of temporary mechanical circulatory support in cardiogenic shock following acute MI have been provided by the AHA.[308]

There had been evidence that LVAD may improve clinical outcomes of patients with AMI and heart failure who do not respond sufficiently to conventional therapy,[309] but percutaneous mechanical circulatory support by the Impella device did not produce a better outcome compared to that of intra-aortic balloon pumping in post-MI cardiogenic shock.[310] Percutaneous short-term active mechanical support devices, in general, do not improve mortality in this setting probably due to an excess of complications such as bleeding.[311, 312] In patients who have undergone successful primary angioplasty, shock is less refractory when

arterial pressure is supported with norepinephrine rather than with epinephrine.[313] The mean arterial pressure should be kept between 85 to 100 mm Hg.[314]

Hospital survivors of AMI who had cardiogenic shock have a higher risk of death and/or hospitalization during the first year after discharge. The risk is time-dependent and is clustered in the early post-discharge period, after which the prognosis is similar in patients with and without cardiogenic shock.

Right Ventricular Infarction

Patients with inferior STEMI and hemodynamic compromise should be assessed with a right precordial V_{4R} lead to detect ST-segment elevation and an echocardiogram to screen for RV infarction. Predominant RV shock represents 5% of all cardiogenic shock cases.[299]

The following principles apply to therapy:

a. Early reperfusion should be achieved if possible.

b. AV synchrony should be achieved, and bradycardia should be corrected.

c. RV preload should be optimized, with initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low.

d. RV afterload should be optimized, with therapy for concomitant LV dysfunction.

e. Inotropic support should be used for hemodynamic instability not responsive to volume challenge.[315]

Finally, it is reasonable to delay CABG surgery for 4 weeks to allow recovery of contractile performance.

Acute mitral regurgitation Recommendations for mechanical complications of STEMI are provided in Table 27 and Figure 15.

Acute MR, in particular, is due to papillary muscle dysfunction or rupture or chordal rupture (see also Valve Disease). Its incidence has declined in the reperfusion era (range, 0.05%–0.26%), but the reported hospital mortality rate remains high, 10-40%.[298] The mitral valve is supported by 2 papillary muscles, the anterolateral branch that has a dual arterial blood supply from the LAD and the diagonal or marginal branch of the circumflex coronary artery, and the posteromedial papillary muscle that has a single blood supply from the circumflex coronary artery or the right coronary artery, depending on dominance. Thus, anterolateral papillary muscle rupture is extremely uncommon and posteromedial papillary muscle rupture typically occurs in association with inferior or lateral STEMIs. Transverse rupture of a papillary muscle is rare and usually fatal. Most commonly there is rupture of the tip of the muscle or a chord and may be due to a relatively small inferior (RCA or Cx) infarct, usually 1-7 days after the infarction. Risk factors include older age, female sex, a history of heart failure, chronic kidney disease, and delayed reperfusion.[298] The murmur is usually soft but the ensuing pulmonary oedema is gross.

Severe MR developing early after MI is associated with increased risks of heart failure and mortality.[316] Emergency mitral valve replacement is the treatment of choice, but repair, typically for patients with partial rupture and stable hemodynamics, can be considered by surgeons with technical expertise in mitral valve repair.[298] Early intervention may mitigate the poor prognosis associated with conservative therapy in patients with post-MI MR. Percutaneous mitral valve repair can serve as an alternative for surgery in reducing MR for high-risk patients.[317]

Ventricular septal rupture

In the contemporary era, early revascularization strategies have effectively decreased the incidence of post-AMI VSR from ~2% to ~0.2%.[318-320] Risk factors include older age, female sex, and delayed reperfusion. Patients have multivessel disease and anterior MI (apical rupture) or inferior MI (basal rupture with worse prognosis). They develop shortness of breath and hypotension and a harsh holosystolic murmur with thrill (50%) may be present. A 12-lead ECG may identify ongoing ischemia, evolving myocardial infarction, Q wave in the affected territory (anterior or inferior), and associated ventricular arrythmias.[298] Biventricular failure generally ensues within hours or days and the murmur and thrill are attenuated. It is often associated with AV block or RBBB. Diagnosis is made by transthoraric or transoesophageal echocardiography that reveals the defect, and probably a dilated RV. Acutely rising mixed venous O_2 saturations in patients with a pulmonary catheter should raise the suspicion of rupture.

Untreated cases have a mortality rate close to 100%.[319] Immediate afterload reduction with or without periprocedural temporary mechanical support is the mainstay of initial therapy (Table 27). Early surgery for repair and concomitant coronary bypass in patients with cardiogenic shock and respiratory failure is associated with 40% mortality. It probably improves survival but is difficult because of friable tissue for the first 6 weeks after the infarction. A 2021 AHA statement suggests delaying surgery when feasible in a hemodynamically stable patient without respiratory failure.[298] Percutaneous closure with VSD-specific devices in VSDs<15 mm,[321] or hybrid percutaneous/surgical approaches,[322] are also available. Surgical and percutaneous repair are viable options with no difference in post-discharge long-term mortality between patients, but in-hospital mortality is lower for surgery.[323]

Myocardial free wall rupture

Ventricular free-wall rupture is a rare, but potentially fatal, complication of acute myocardial infarction, requiring prompt surgical intervention.[324] More commonly occurs in the elderly with hypertension, after large anterior MI and particularly following expansion. Usually it occurs 1 day after infraction (up to 7 days without reperfusion). Although free wall rupture is

the most commonly reported mechanical complication of AMI, its true incidence is unknown because it usually presents as out-of-hospital sudden cardiac death and there is a lack of routine autopsy.[298]

Acute free wall rupture is associated with hemopericardium and electromechanical dissociation and is fatal. Subacute rupture (25%), ie sealing of the rupture with thrombus or adhesions (**pseudoaneurysm**), may lead to a relatively stable hemopericardium that allows time for surgical intervention. Patients with tamponade but without electromechanical dissociation may have a good prognosis with percicardiocentesis and conservative management. When pericardial effusion in a parasternal short-axis view exceeds 10 mm, the risk of free wall rupture is high and pericardial aspiration for measurement of hematocrit in the effusion is useful.[325] Moderate pericardial effusions without tamponade carry the risk of late rupture. Patients with free-wall rupture should be considered for urgent cardiac surgical repair, and CABG should be undertaken at the same time as repair of free-wall rupture.
True LV aneurysm may result in intractable VT and/or pump failure and these cases surgery with concomitant CABG is indicated.

Pericarditis

Pericardial effusions are more common after anterior MI and when congestive failure is present (Table 28). Usually of no prognostic significance although it may take months to resorb.
Pericarditis may develop and resolve as late as 6 weeks after MI. The pain typically radiates to either edge of trapezius ridge and becomes worse with deep inspiration. Anticoagulants are stopped if not necessary and aspirin is the treatment of choice (Table 29). In non-responders even to higher doses of aspirin, colchicine 0.6 mg/12h po, acetaminophen, or narcotic analgesics may be given. NSAIDs and steroids have been associated with increased risk of scar thinning and myocardial rupture. ***Dressler syndrome*** (fever, leucocytosis, elevated ESR, and pericarditis with effusion due to anti-cardiac antibodies) 1 to 8 weeks after non-reperfused MIs, is now rarely seen.

Thromboembolic Complications

The incidence of **LV thrombus** following anterior MI is 4-15% and these patients may require anticoagulation in addition to antiplatelet therapy for 6 months or even more.[326] Regression of thrombus (usually within 3 months on oral anticoagulation) is associated with lower mortality, but in about one-third of cases, thrombus does not resolve despite anticoagulation with or without antiplatelet therapy.[327, 328] Patients with or without acute ischemic stroke who have a cardiac source of embolism (atrial fibrillation, mural thrombus, or akinetic segment) should receive moderate-intensity (INR 2 to 3) warfarin therapy (in addition to aspirin).

Bleeding

Bleeding has an ominous prognosis with mortality increasing as bleeding severity increases (Table 29).[329-332] Several definitions and classifications of bleeding have been used in trials,[330, 332] with the simplest one provided by TIMI (Table 30). Major bleeding is associated with 4-fold increase in the risk of death (4-fold), MI (5-fold) and stroke (3-fold). Bleeding risk is increased with higher or excessive doses or combinations of antithrombotic agents switch between different anticoagulant drugs, invasive procedures, and length of treatment, as well as with older age, reduced renal function, low body weight, female gender, and baseline haemoglobin (Table 31).[333] In patients undergoing PCI, bleeding is associated with increased in-hospital mortality that is highest with non-access site bleeding.[334] Any gastrointestinal or genitourinary bleeding is associated with higher rates of new cancer diagnosis, and should prompt investigation for cancers at these sites.[335]

Minor bleeding should preferably be managed without interruption of active treatments.

Major bleeding requires interruption and/or neutralization of both anticoagulant and antiplatelet therapy and platelet transfusion, unless bleeding can be adequately controlled by specific haemostatic intervention. The risk of acute thrombotic events after interruption of antithrombotic/antiplatelet agents is maximum after 4–5 days, but persists for up to 30 days.[336]

Blood transfusion may be needed for severe bleeding (haematocrit <25% or haemoglobin <7 g/dL). There has been evidence for a 20% relative risk increase with blood transfusion or a liberal blood transfusion strategy compared with a strategy of no transfusion or restricted transfusion in the setting of STEMI,[337] probably due to increased platelet aggregation,[338] but this may due to selection bias with transfusions needed in more seriously ill patients. [339] Blood transfusion should be withheld in haemodynamically stable patients with haematocrit >25% or haemoglobin level >7 g/L.[337]

Aspirin **and** ***clopidogrel*** are irreversible platelet inhibitors. Their action is slowly reversed by the continuous generation of new platelets (around 10–20% per day), so antiplatelet effects persist for 5–10 days after cessation of treatment. Platelet transfusion is the only possibility to reverse the effects of clopidogrel/aspirin. The recommended minimum dose in adults is 0.5–0.7x10^{11} platelets/7 kg of bodyweight. ***Unfractionated heparin*** can be inhibited by an equimolar concentration of protamine sulfate (1-1.5 mg/100 USP units of heparin, not to exceed 50 mg). Protamine only partially affects anti-Xa levels, and may be used in reversing bleeding associated with *LMWH* but not with ***fondaparinux***. For antidotes to x (Xa inhibitors see Chapter 53. There is no antidote for ***bivalirudin***. Its plasma half-life is 25 min and is partially cleared renally. Platelet transfusion is needed with ***abciximab***. Interruption of ***eptifibatide*** and ***tirofiban*** infusion allows platelet function within 4-8 h. In emergencies,

fibrinogen supplementation with fresh frozen plasma or cryoprecipitate with or without platelet transfusion are recommended for immediate reversal of the effects of eptifibatide and tirofiban. Recommendations for preventive strategies are provided in Table 30.

Thrombocytopenia

Thrombocytopenia is defined as a platelet count <150 x 10^9/L that can be expected in up to 13% of patients with an ACS. It is considered moderate when the platelet count is 50-100 x 10^9 , and severe when <50 x 10^9. [340, 341]

Immune-mediated heparin-induced thrombocytopenia (HIT) is defined as a decrease in platelet count to <100 000/mL or a drop of >50% from baseline platelet count following heparin exposure.

Nonimmune heparin-associated thrombocytopenia is a mild, transient decline in platelet count that occurs 1 to 4 days after initiating heparin in 10% to 20% of patients. It rarely leads to a severe reduction in platelet levels and resolves spontaneously, despite continuation of UFH.

Pseudothrombocytopenia is a laboratory artifact due to platelet clumping in EDTA-containing tubes and can be avoided by the use of citrate instead of EDTA for blood sampling.

Immune-mediated HIT is a serious complication that often leads to severe thrombo-embolic events. [342] It is not dose-dependent, usually causes a severe drop in platelet levels (<50%) and typically appears 5–10 days after the start of UFH treatment, but much earlier in patients with recent (within 3 months) UFH exposure. Delayed-onset HIT occurring several days or weeks after the cessation of UFH treatment has also been described. HIT is a hypersensitivity reaction to heparin mediated via an IgG antibody to platelet factor 4. This IgG/heparin/platelet factor 4 complex binds to platelets and cross-links their receptors, which causes platelet activation and thrombosis. Bleeding is rare. HIT occurs in 0.5% to 5% of patients treated with unfractionated heparin (3000 to 30,000 daltons) and <1% with LMWH (less antigenic, 2000 to 9000 daltons).

Thrombocytopenia is very rare with *bivalirudin* and negligible with *fondaparinux*,[343] despite weak binding to the platelet factor 4 antigen. It has been reported to occur with *abciximab* (2.5%) and less with *tirofiban* (0.5%) or *eptifibatide* (0.2%). Rarely it may also occur with *clopidogrel*.[344] All patients diagnosed with thrombocytopenia or a thrombotic complication within 4 to 14 days after starting heparin therapy should have heparin discontinued immediately and screening tests performed.

Quinine- or other *drug-induced* immune thrombocytopenic purpura, as well as glycoprotein IIb/IIIa antagonist–induced thrombocytopenia, typically has more severe thrombocytopenia than that of HIT. Patients with massive, acute venous thromboembolism occasionally develop thrombocytopenia because of platelet consumption on the thrombus

surface; their platelet count nadir usually happens within 1 day of heparin initiation. Other causes of repeat thrombotic episodes are the *anti-phospholipid antibody syndrome, Trousseau's syndrome, cholesterol emboli syndrome*, *and infective or nonbacterial thrombotic endocarditis*. HIT should be also considered if a recently hospitalized patient returns with thromboembolism). Mortality associated with HIT has been reported 5-30%.[343] [340]

Diagnosis

Several scoring systems have been proposed. The most practical ones are the *4Ts*, and the *post-CPB (cardiopulmonary bypass)* scoring system (Table 31). Thromboembolic complications are predominantly venous and may be devastating; pulmonary embolism, deep-vein thrombosis, myocardial infarction, and stroke may occur. Diagnosis is confirmed by *circulating heparin-PF4 antibodies* that may remain detectable for up to 4 months after the diagnosis of HIT in 10% to 40% of patients, depending on the assay used. These tests have a high negative predictive value but a low positive predictive value.[342] The diagnostic approach to HIT is further enhanced by combining the results of immunologic testing with a functional (platelet activation) assay. These tests measure platelet activation from the heparin PF4-antibody complex by mixing donor platelet-rich plasma with patient plasma and heparin.[340]

Therapy

Interruption of heparin (UFH or LMWH) is warranted in the case of documented or suspected HIT (Table 33). Significant thrombocytopenia (<100,000/mL or >50% drop in platelet count) occurring during treatment with GP IIb/IIIa inhibitors and/or heparin (LMWH or UFH) requires the immediate interruption of these drugs. Very severe thrombocytopenia (<10,000/mL) induced by GP IIb/IIIa inhibitors requires platelet transfusion with or without fibrinogen supplementation with fresh frozen plasma or cryoprecipitate in the case of bleeding. Routine platelet transfusion in all patients is not recommended.[340]

In the case of thrombotic complications, anticoagulation can be achieved with a direct thrombin inhibitor such as ***bivalirudin***. This is also recommended by the ACCP 2012 guideline on antithrombotic therapy (2C) for cardiac surgery or coronary intervention. [345, 346] The direct thrombin inhibitor ***argatroban*** (IV infusion of 2.0 mcg/kg/min; 0.5-1.2 mcg/kg.min in liver disease, critical illness or after cardiac surgery to maintain an APTT of 1.5-3.0 times baseline value - max 10 mcg/kg/min) is approved by the FDA for HIT, and is particularly indicated in renal insufficiency (ACCP 2012-2C). Hypercoagulability may occur with discontinuation of the drug, and transition to warfarin may be challenging.

The factor Xa inhibitor ***danaparoid*** and the direct thrombin inhibitor ***lepirudin*** are also recommended by the ACCP 2012 guidelines (2C). Danaparoid is recommended in pregnancy (ACCP 2012-2C). However, danaparoid access has been limited and lepirudin has

been recalled from the market. ***Fondaparinux,***[347] and other ***direct oral anticoagulants***, [348] may also be used.

Platelet glycoprotein IIb/IIIa inhibitors reduce thrombin generation indirectly and inhibit platelet aggregation. However, they lack direct anticoagulant effects and do not inhibit Fc receptor–mediated activation of platelets by HIT antibody.

Platelet transfusions are recommended by the ACCP for invasive procedures (ACCP 2012-2C). They should not be used routinely for prophylaxis of bleeding in HIT because they may exacerbate the hypercoagulable state, leading to additional thrombosis. [340]

Vitamin K inhibitors such as warfarin are started when platelets are >150 x 10^9/L (ACCP 2012-1C). Early introduction should be avoided due to the potential to worsen the prothrombotic state through a rapid reduction of protein C, and an overlap period to allow a therapeutic INR should intervene. Warfarin should be continued for 4-6 weeks, and in patients with thrombosis for 3 months.

Patients with a history of HIT may not invariably have recurrent HIT on heparin reexposure. In addition, heparin has been tolerated for a brief period, such as during cardiac surgery, in patients in whom heparin-PF4 antibodies have fully waned. Still it is better to use an alternative anticoagulant.

Argatroban, lepirudin and bivalirudin are FDA-approved agents for patients with HIT requiring PCI.

Conversion to oral anticoagulation

According to ACCP guidelines, a transition to warfarin therapy is required for 3 months in patients with HITT and 4 weeks in those with isolated HIT. Initiation of therapy should be delayed until the platelet count has recovered to at least 150 x 109 /l, because concurrent thrombocytopenia may reflect the ongoing prothrombotic state of HIT.[346]

Re-exposure to heparin

Typically, the heparin-dependent antibodies fall to undetectable levels after 50 to 85 days. Thus, once antibodies are no longer present, the AACP guidelines recommend the (short-term) use of heparin for cardiac surgery patients with histories of HIT. However, for patients with histories of HIT undergoing PCI, the recommendation is to use a nonheparin anticoagulant agent.[346]

Antiplatelet therapy in patients with thrombocytopenia

Management strategies for these patients are also presented in Figure 16.

Specific Clinical Settings

Patients with non-obstructive coronary arteries

Patients with myocardial infarction may have non-obstructive coronary arteries disease (ie stenoses <50%) (Myocardial infarction with non-obstructive coronary arteries- **MINOCA).**

This occurs in 5% to 10% of all patients with acute MI and is usually seen in younger patients and women (see also Chapter on Epidemiology and Pathophysiology).[349-352] Most women with MINOCA (up to 64%) have a final diagnosis of myocardial infarction.[353] Coronary artery spasm may be inducible in 27% of patients myocardial infarction and non-obstructive coronary arteries, and thrombophilia disorders are detected in approximately 14%.[352] Thrombophilia testing is not necessary, but in certain patients antiphospholipid antibody testing, and investigations for conditions such as heparin-induce thrombocytopenia, paroxysmal nocturnal haemoglobinuria, and other rare disorders may be considered.[354] The prognosis has been long debated, and seems to depend on the underlying cause. Long-term treatment with statins and renin-angiotensin system blockers may be beneficial, whereas β-blockers and dual antiplatelet therapy seem less likely to reduce the risk of new cardiovascular events.[349] Beta blockers are contraindicated in patients with coronary spasm.[355] Recommendations are provided in Table 32 and Figures 17 and 18.

Spontaneous Coronary Dissection

Spontaneous coronary dissection may be the cause of 1-4% of acute coronary syndromes, but the incidence is reported to be much higher (22-35% of ACS) in women <60 years of age, in pregnancy-related MI, and in other conditions (see Chapter on Epidemiology and Pathophysiology. In cases of diagnostic uncertainty after angiography, the use of intracoronary imaging with OCT or IVUS has to be carefully considered (Figure 16). Its initial presentation can be severe, with cardiogenic shock in 2-5%, and ventricular arrhythmias or sudden cardiac death in 3-11%. [356-360] Conservative therapy with antiplatelet agents but not anticoagulation, is favored, except for patients with unstable symptoms, hemodynamic instability, or left main dissection. Thus, routine revascularization should not be performed, but in patients with hemodynamic instability or ongoing ischemia despite conservative therapy, revascularization may be considered (Table 33).[177] Following SCAD, discharge on oral anticoagulation and treatment with DAPT comprising aspirin and the more potent $P2Y_{12}$ inhibitor, ticagrelor, have been independently associated with a higher risk of MACE, and single may be superior to dual antiplatelet therapy.[361, 362] Acute survival is good but long-term events are frequent, including recurrent dissection and follow-up of these patients is advisable. [356-360] PCI is associated with favorable 3-year survival, but may require left main revascularization, mechanical circulatory support, or emergent coronary bypass graft surgery.[363]

Perioperative MI

Perioperative MI has a high mortality rate of 10-14%, and 30% of patients who survive will be rehospitalized within the next 6 months.[364, 365] Bleeding event, peak troponin T level, and peripheral vascular, older age, and renal dysfunction predict mortality within 30 days of PCI

in this patient population. [366] Diagnosis and management are presented in Figures 17 and 18. Recommendations for the timing of non-cardiac surgery and revascularization in patients with ACS are provided in Table 34.

Comorbidities in ACS

Recommendations for comorbidities in ACS in general are presented in Table 35.

Diabetics

All patients with ACS should be screened for diabetes (Table 36). Tight glycaemic control to achieve normoglycaemia is no more recommended. Instead, insulin infusion to maintain glucose levels <180 mg/dl while avoiding hypoglycemia (>90 mg/dl) is recommended by ACCF/AHA. However, intensive glucose regulation aiming at a plasma glucose level of 85 to 110 mg/dL by using intravenous insulin, did not reduce infarct size in non-insulin dependent hyperglycemic (up to 288 mg/dL) patients with ACS treated with PCI as compared to conventional expectative glucose management, and was associated with harm.[367] An early invasive strategy is probably beneficial for diabetic patients with NSTE-ACS,[158] and DES are preferred to BMS. CABG is preferable to PCI in multivessel disease.

Chronic Kidney Disease

Renal function should be assessed with creatinine clearance (CrCl) estimation in all patients with ACS (Table 37). Chronic kidney disease (defined as estimated creatinine clearance [CrCl] <60 mL·min−1·1.73 m−2) has a prevalence of 42.9% among patients presenting with non–ST-segment–elevation myocardial infarction.[96] It depends on the patient's pre-existing renal condition and the amount of contrast volume used, but risk is complex, and can be predicted by a model.[368] An 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). Drug dosage adjustments have been recently reviewed by AHA.[96] In patients on dialysis clopidogrel, when needed, is probably preferable to other $P2Y_{12}$ receptor blockers.[369] Recommendations for the management of patients with **renal failure** are presented in Table 37. Chronic kidney disease (defined as estimated creatinine clearance [CrCl] <60 mL·min−1·1.73 m−2) has a prevalence of 30.5% among patients presenting with ST-segment–elevation myocardial infarction.[96] Coronary angiography and revascularization are recommended, with adequate measures to reduce the risk of acute kidney injury (ACC/AHA/SCAI 2021 GL on revascularization, I C-EO).

Anemia

Anemia is a marker of ischemic and bleeding events and hemoglobin measurements are mandatory on presentation. Blood transfusion is recommended only with Hct<25% or

Hb<8g/dl (Table 38).[370] The use of erythropoiesis-stimulating agents is not recommended in patients with mild to moderate anemia and coronary heart disease.[371]

Elderly

Patients older than 75 years of age should be investigated at low level of suspicion due to often atypical presentation of ACS, usually with the same interventional strategies as younger patients.[178] In an individual patient data meta-analysis on 1479 patients >70 years old, a routine invasive strategy was superior to conservative approaches in reducing the risk of myocardial infarction and urgent revascularization at one year, although it did not reduce the risk of a composite of all-cause mortality and MI within 1 year.[372] In the After Eighty study, an invasive strategy was also beneficial in patients aged more than 80 years, although this was not clear for patients more than 90 years of age.[147] In the SENIOR-NSTEMI cohort study based on routine clinical data the survival advantage of invasive compared with non-invasive management appears to extend to patients with NSTEMI who are aged 80 years or older.[373] In the elderly, primary PCI is preferable to fibrinolysis,[374] and complete revascularization is beneficial.[239] Care is needed due to increased risk of bleeding and possibly concurrent renal dysfunction in this group and drug dosages should be modified accordingly (Table 39). It should be noted, however, that despite the large impact of cardiovascular disease on quality of life, morbidity, and mortality in older adults, patients aged ≥75 years have been markedly underrepresented in most major cardiovascular trials.[374, 375]

Young Patients

Nearly 30% of patients ≤50 years of age with STE MI have LVEF <50%, and in more than one-half of such cases, EF remains below 50% 6 months post-MI (YOUNG-MI Registry).[376]

Familial Hypercholesterolaemia

Patients who develop an ACS before the age of 55 years or even earlier and in the absence of other high-risk factors, should be considered for familial hypercholesterolemia.[377] Diagnosis and management are discussed in detail in Chapters on Epidemiology and Prevention of CAD.

HIV-positive patients

HIV-positive patients have a worse prognosis following an ACS, especially when receiving protease inhibitors,[378] and increased platelet reactivity before and after treatment with aspirin and $P2Y_{12}$.[379]

Cancer

Recommendations for patients with cancer who develop an ACS have been published by the ESC (Table 40).[380] See also Cardio-oncology.

Noncardiac Surgery

Recommendations are provided in Figure 19 as well as in the relevant section on Noncardiac Surgery.

Pregnancy

Medical therapy is indicated in patients without high risk criteria, and PCI for high risk cases (Table 41).[381, 382] Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin due to a lack of data. Pregnancy-related complications such as preeclampsia and gestational diabetes mellitus are associated with triglyceride levels >250 mg/dL.[383] A heart healthy lifestyle (diet, exercise, weight management) is recommended for all patients. Those with very high triglyceride levels (>500 mg/dL) are at risk for pancreatitis and may benefit from pharmacological agents (omega-3 fatty acids with or without fenofibrate or gemfibrozil) during the second trimester. The risk for premature atherosclerosis is elevated in patients with familial hypercholesterolemia, and during pregnancy, but statins are contraindicated during pregnancy. Current treatment options for pregnant women with familial hypercholesterolemia include bile acid sequestrants, which lack systemic circulation, and, as last resort, low-density lipoprotein apheresis in severe cases.[383]

Pregnancy is associated with a three- to four-fold increase in STEMI risk compared with age-matched non-pregnant women.[384] The aetiology of CAD in pregnancy differs from the general population, and the majority has non-atherosclerotic mechanisms, including pregnancy-related spontaneous coronary artery dissection (43%), angiographically normal coronary arteries (18%), and coronary thrombosis (17%). Thus, blinded fibrinolysis is not recommended. Furthermore, recombinant tissue plasminogen activator does not cross the placenta but may induce bleeding complications (subplacental bleeding). Apart from heparin and aspirin, clopidogrel may also be used but data on their safety is limited.[385] Pregnancy-related spontaneous coronary artery dissection is the most common cause of pregnancy-associated myocardial infarction.[386] It is a rare and potentially lethal complication of pregnancy. It is estimated that 1 in 16000 pregnancies is complicated by acute myocardial infarctions in the US, and up to one fourth of these are due to spontaneous coronary dissection. [387] Percutaneous coronary intervention is associated with low success rate and high likelihood of complications, and coronary artery bypass surgery is often required.[388]

Risk Stratification Before Discharge

Stable patients can be transferred from the CCU after 12-24h and mobilization is allowed. Arrhythmia monitoring should be initiated immediately after presentation, continuing uninterrupted ≥12–24 h, and ≥24–48 h in patients without revascularization until there is no evidence of ongoing ischaemia.[389] Stable patients can be safely discharged as early as 48 h following reperfusion, and physical activity is gradually

resumed.[390] ***Echocardiography*** for assessment of LVEF is essential. The LVEF should be reassessed 40 days after MI in nonrevascularized patients and 90 days after revascularization in revascularized patients.[391] With proper reperfusion, significant LVEF improvement may be seen one month after STEMI.[392] The risk of stroke is increased in patients with reduced left ventricular ejection fractions even in the absence of AF. Advanced age, prior stroke, a history of hypertension, Killip class 3 or 4, and eGFR ≤45 ml/min/1.73 m^2, are specific risk factors.[393] Persistent impairment of ventricular function to this degree is associated with greater total and CV mortality over the next decade.[376] Following a STEMI, the risk of subsequent cardiovascular events is highest in the first year, with recurrent MI in 10% of patients with an approximate cardiovascular mortality of 5%. It remains elevated at least 3 years after MI, indicating a need for prolonged surveillance, particularly in patients with additional risk factors.[394] In primary PCI-treated STEMI, patients surviving the first 90 days have 10-year mortality that is 2% higher than that of a matched general population.[395] A left dominant coronary artery system is associated with a significantly increased risk of 30-day mortality, and early reinfarction after STEMI. After surviving the first 30-days post-STEMI, coronary vessel dominance had no influence on long-term outcome.[396]
Recommendations are provided in Tables 42 and 43.

Long-term therapy

Recommendations are provided in Tables 42-45, and Figures 21-23. ***Aspirin*** (75-100 mg) should be continued indefinitely, and a ***PY12 inhibitor*** should be added for 12 months. However, the optimal duration of ***dual antiplatelet therapy*** (DAPT) is controversial (see also Chapter on revascularization).[127, 397-402] Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor has been shown to reduce the risk of major adverse cardiovascular events compared with aspirin alone after PCI or acute coronary syndrome but with increased risk of bleeding.[403] However, in the TACSI RCT, among patients who underwent CABG for an acute coronary syndrome, ticagrelor plus aspirin did not result in a lower incidence of death, myocardial infarction, stroke, or repeat coronary revascularization than aspirin alone at 1 year.[404] De-escalation from potent P2Y12 inhibitors to low-dose potent P2Y12 inhibitor or clopidogrel at 1 month, during a 12-month course of DAPT, might be considered the optimal regimen to improve outcomes in patients with acute coronary syndrome, while discontinuation of aspirin with continued $P2Y_{12}$ inhibitor monotherapy has been found to reduce the risk of bleeding without increasing major adverse cardiovascular events when stopped 1 to 3 months after PCI.[405-408] However, discontinuation of aspirin as early as 4 days after PCI resulted in increased rate of stent thrombosis (NEO-MINDSET RCT).[409] In patients

requiring infinite antiplatelet therapy, clopidogrel may be superior to aspirin alone,[410, 411] but this has not been verified in all trials.[412]

Continuation of DAPT beyond 12 months may be considered in certain cases (bifurcation stenting, long stents etc), and especially in diabetics. [413, 414] Patients with *renal* dysfunction also derived higher benefit from long-term ticagrelor administration.[415] In patients with a myocardial infarction 1-3 year previously, and high risk for ischemic events, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding over a 33-month follow-up. A dose of 60 mg bd had a better benefit-risk profile than 90 mg bd (PEGASUS-TIMI 54).[416] This benefit is more pronounced in patients with multivessel disease,[417] and in those without prior stenting due to their higher baseline risk.[418] Similar conclusions about the benefit of extended dual antiplatelet therapy without any excess in fatal or intracranial bleeding in patients with a previous MI, were reported by other sudies.[419] [420] However, in patients at low risk for cardiac events but at high risk for bleeding the benefit-risk balance may be unfavorable.[421] Concomitant use of selective serotonin uptake inhibitors increases the risk of bleeding in patients on DAPT.[422]

In patients with AF, NOAC monotherapy is safe one year after stenting.[423]

Rivaroxaban, but not apixaban or dabigatran has reduced ischemic events but at an increased risk of bleeding.[109, 114, 117] However, **milvexian** an oral factor XIa inhibitor, did not decrease the risk of cardiovascular death, myocardial infarction, or ischemic stroke but did not increase the risk of intracranial or fatal bleeding, as compared with placebo.[424] ***Vorapaxar***, an inhibitor of the protease-activated receptor PAR-1 through which thrombin activates platelets , reduces the risk of major cardiovascular events when added to aspirin and clopidogrel, and particularly in diabetics, but at increased risk of bleeding.[425, 426] It is FDA approved for secondary prevention in patients with a history of MI or peripheral arterial disease but not a previous stroke or TIA. ***If oral anticoagulants*** are indicated they may be combined with aspirin and thienopyridines but at an increased risk of bleeding. In patients with a clear indication for oral anticoagulation (e.g. atrial fibrillation with CHA2DS2-VASc Score ≥2 or mechanical valve prosthesis), oral anticoagulation must be implemented in addition to antiplatelet therapy, but the duration of antiplatelet therapy should be restricted to one year.[427] The lowest efficacious INR (2-2.5) should be targeted. In patients with left ventricular thrombus, anticoagulation should be instituted for a minimum of 3 months. ***Statins*** provide substantial reductions in mortality as well as in non-fatal ischaemic events (see also Chapter 28). Proprotein convertase subtilisin kexin type 9 inhibitors ***(PSK9)*** have been found beneficial after an ACS,, and the addition of PSK9 to high-intensity statin therapy has resulted in significantly greater coronary plaque regression in non-infarct-related arteries.[428] Polypill strategies (ie combining aspirin, a statin and an ACE inhibitor) may

improve adherence to medication.[429] The addition of ***ezetimibe*** to statin therapy may decrease the risk of non-fatal MI and stroke,[430] and is safe in patients >75 years old.[431]

The relative benefit of ***beta blockers*** after myocardial infarction in the context of more aggressive revascularisation is less clear in patients without LV dysfunction, and this is also reflected in recommendations by the ACC/AHA and ESC guidelines. COPD is not a contraindication for their use.[432] Previous trials that mainly involved patients with large myocardial infarctions and left ventricular systolic dysfunction, have shown that long-term beta-blocker therapy after myocardial infarction reduces mortality by approximately 20%.[433] In the recent REDUCE-AMI RCT on patients with acute myocardial infarction who underwent early coronary angiography and had a preserved left ventricular ejection fraction (≥50%), long-term beta-blocker treatment did not lead to a lower risk of the composite primary end point of death from any cause or new myocardial infarction than no beta-blocker use.[434] Also in the REBOOT-CNIC RCT, on patients with a myocardial infarction and a left ventricular ejection fraction above 40%, beta-blocker therapy had no effect on the incidence of death from any cause, reinfarction, or hospitalization for heart failure,[435] and in the SMART-DECISION RCT discontinuation of beta-blocker therapy was noninferior to continuation beyond a year after STEMI.[436] A sex-specific subanalysis of the REBOOT also suggested potential harm in women with preserved EF and receiving high doses of beta blockers,[437] and a pooled analysis of the ABYSS and SMART DECISION RCTs on stable patients with previous myocardial infarction and left ventricular ejection fraction ≥40%, discontinuation of beta blockers approximately 3 years after the MI was not inferior to continuation of therapy.[438] However, in an individual patient meta-analysis, in patients with acute myocardial infarction with mildly reduced LVEF (40-49%) without history or clinical signs of heart failure, β-blocker therapy was associated with a reduction in the composite of all-cause death, new myocardial infarction, or heart failure.[439] In the BETAMI-DANBLOCK RCT among patients with a myocardial infarction and a LVEF of at least 40%, beta-blocker therapy led to a lower risk of death or major adverse cardiovascular events than no beta-blocker therapy.[440] Furthermore, in the ABYSS RCT, interruption of long-term beta-blocker treatment after at least 6 months after myocardial infarction was not shown to be noninferior to a strategy of beta-blocker continuation with respect to a composite outcome of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization, nor did it seem to improve quality of life.[441] However, in a secondary analysis of the ABYSS RCT, higher baseline heart rate under β-blocker therapy was associated with increased risk of major cardiovascular events and mortality in stable post–myocardial infarction (MI) patients with left ventricular ejection fraction ≥40%.[442] Thus, in stable post-MI patients with preserved

or mildly reduced left ventricular ejection fraction, discontinuation of well-tolerated β-blocker therapy should be approached cautiously.

Angiotensin-converting enzyme inhibitors or ***angiotensin II receptor blockers*** are probably indicated in all patients regardless of the presence of reduced LV function,[443] and especially in reduced LVEF. In the absence of severe renal dysfunction (creatinine>2.5mg/dl) or hyperkalaemia, post-myocardial infarction patients with an ejection fraction of less than 40% or heart failure should receive an ***aldosterone antagonist***, such as eplerenone.[444] Anti-inflammatory therapy with monoclonal antibodies that inhibit the interleukin-6 receptor (IL-6) has been promising. ***Canakinumab*** at a dose of 150 mg subcutaneously every 3 months has resulted in a significantly lower rate of recurrent cardiovascular events over a period of 48 months, in patients with a prior MI and CRP>2mg/L.[445] ***Tocilizumab*** has also increased myocardial salvage in patients with acute STEMI.[446] ***Colchicine***, 0.5 mg od had been found beneficial in patients with stable or unstable CAD in a previous meta-analysis.[447] Subsequent RCTs have refuted a benefit in post-MI patients. In the COVERT-MI RCT high-dose colchicine at the time of reperfusion and for 5 days did not reduce infarct size assessed by cardiac magnetic resonance imaging.[448] In the CLEAR RCT, colchicine, when started soon after myocardial infarction and continued for a median of 3 years, did not reduce the incidence of the composite primary outcome (death from cardiovascular causes, recurrent myocardial infarction, stroke, or unplanned ischemia-driven coronary revascularization).[449] Similar negative results were found for its use in patients with ischaemic stroke.[450, 451] ***Non-steroidal anti-inflammatory*** drugs (NSAIDs), with as little as 3 days of use, increase the risk of bleeding, especially on patients on 2 or 3 antithrombotic regiments.[452] Steroids or NSAIDS given early after MI can also cause tissue thinning and MI expansion. ***Influenza vaccination*** should be provided to all patients with CAD, especially after MI.[453] ***Smoking cessation*** is essential, and ***varenicline***, a nicotinic acetylcholine receptor partial agonist, can be safely used to assist smoking abstinence.[454] All patients should be screened for ***depression***,[455] following an ACS. ***Exercise-based rehabilitation*** is beneficial and should commence 8-12 after the acute event.[456] Moderate (but not intense) exercise is also allowed in patients with spontaneous coronary artery dissection and fibromuscular dysplasia.[457] ***Chelation therapy*** is not recommended. There has been some recent evidence that it might be beneficial in combination with high-dose vitamins in post-MI patients.[458] ***Sexual activity*** is allowed >=1 week after uncomplicated MI, provided that the patient has no symptoms during mild to moderate physical activity. [459] A rehabilitation program is necessary (see ESC 2026 GL on rehabilitation).[460] Adopting ***healthy dietary patterns*** confers benefits for the secondary prevention of deaths among MI survivors.[461]

Since the discovery that the heart is not a post-mitotic organ and myocardial tissue regeneration is possible, ***stem cell transplantation*** using autologous bone marrow

mononuclear cells that mainly contain hematopoietic, mesenchymal and endothelial stem cells has used them for myocardial regeneration after myocardial infarction. Increases in LVEF and reduction of infarct size have been shown, but mortality benefits are not established [462] [463] Stem cell transplantation may be a promising therapeutic modality, but several questions regarding its clinical efficacy, mechanism of action, optimal timing of transplantation, and type of cells used remain. Cardiac patches are also a promising therapy for myocardial infarction. These patches consist of scaffolds or loaded therapeutic agents that provide mechanical reinforcement, synchronous electrical conduction, and localized delivery within the infarct zone to promote cardiac restoration.[464]

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