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1. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC) Authors/Task Force Members: Borja Ibanez* (Chairperson) (Spain), Stefan James* (Chairperson) (Sweden), Stefan Agewall (Norway), Manuel J. Antunes (Portugal), Chiara Bucciarelli-Ducci (UK), He´ctor Bueno (Spain), Alida L. P. Caforio (Italy), Filippo Crea (Italy), John A. Goudevenos (Greece), Sigrun Halvorsen (Norway), Gerhard Hindricks (Germany), Adnan Kastrati (Germany), Mattie J. 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References . . . . . .51 Abbreviations and acronyms ACE angiotensin-converting enzyme ACCA Acute Cardiovascular Care Association ACS acute coronary syndrome AF atrial fibrillation ALBATROSS Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up AMI acute myocardial infarction ARB angiotensin II receptor blocker ASSENT 3 ASsessment of the Safety and Efficacy of a New Thrombolytic 3 ATLANTIC Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery ATLAS ACS 2–TIMI 51 Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 ATOLL Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up AV atrioventricular b.i.d. bis in die (twice a day) BMI body mass index BMS bare-metal stent BNP B-type natriuretic peptide CABG coronary artery bypass graft surgery CAD coronary artery disease CAPITAL AMI Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction CCNAP Council on Cardiovascular Nursing and Allied Professions CCP Council for Cardiology Practice; CCU coronary care unit CHA2DS2-VASc Cardiac failure, Hypertension, Age 75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female) CI confidence interval CKD chronic kidney disease CMR cardiac magnetic resonance CPG Committee for Practice Guidelines CRISP AMI Counterpulsation to Reduce Infarct Size Pre- PCI-Acute Myocardial Infarction CT computed tomography COMFORTABLE- AMI Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with acute myocardial infarction trial; Compare-Acute Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease trial CURRENT- OASIS 7 The Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events–Seventh organization to assess strategies in ischaemic syndromes CvLPRIT Complete Versus Lesion-Only Primary PCI Trial DANAMI DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction DANAMI 3- DEFER DANAMI 3 – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction ESC Guidelines 3 Downloaded from by guest on 16 September 2017 4. ..... DANAMI-3– PRIMULTI DANAMI 3 – Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease DAPT dual antiplatelet therapy DES drug-eluting stent EACVI European Association of Cardiovascular Imaging EAPC European Association of Preventive Cardiology EAPCI European Association of Percutaneous Cardiovascular Interventions EARLY-BAMI Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention ECG electrocardiogram ECLS extracorporeal life support ECMO extracorporeal membrane oxygenation eGFR estimated glomerular filtration rate EHRA European Heart Rhythm Association EMS emergency medical system EPHESUS Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study ESC European Society of Cardiology EXAMINATION Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction ExTRACT– TIMI 25 Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction FFR fractional flow reserve FMC first medical contact FOCUS Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention FOURIER Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial. GP glycoprotein GRACE Global Registry of Acute Coronary Events GRACIA Grupo de Analisis de la Cardiopatıa Isque´mica Aguda HDL-C high-density lipoprotein cholesterol HFA Heart Failure Association HR hazard ratio IABP intra-aortic balloon pump ICCU intensive cardiac care unit ICD implantable cardioverter defibrillator IMPROVE-IT Improved Reduction of Outcomes: Vytorin Efficacy International Trial IRA infarct-related artery IU international units i.v. intravenous LBBB left bundle branch block LDL-C low-density lipoprotein cholesterol LGE late gadolinium enhancement LV left ventricle/ventricular LVAD Left ventricular assist device LVEF left ventricular ejection fraction MACE major adverse cardiac event MATRIX Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX METOCARD- CNIC Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction MI myocardial infarction MINOCA myocardial infarction with non-obstructive coronary arteries MRA mineralocorticoid receptor antagonist MVO microvascular obstruction NORSTENT Norwegian Coronary Stent NSTEMI non-ST-segment elevation myocardial infarction NT-proBNP N-terminal pro B-type natriuretic peptide OASIS-6 Organization for the Assessment of Strategies for Ischemic Syndromes o.d. omni die (once a day) PAMI-II Second Primary Angioplasty in Myocardial Infarction PaO2 partial pressure of oxygen PCI percutaneous coronary intervention PCSK9 proprotein convertase subtilisin/kexin type 9 PEGASUS- TIMI 54 Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 PET positron emission tomography PIONEER AF-PCI Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention p.o. per os (orally) PPI proton pump inhibitor PRAMI Preventive Angioplasty in Acute Myocardial Infarction PRODIGY PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY RBBB right bundle branch block REMINDER A Double-Blind, Randomized, Placebo- Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction RIFLE- STEACS Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome RIVAL Radial Versus Femoral Access for Coronary intervention RV right ventricle/ventricular SaO2 arterial oxygen saturation 4 ESC Guidelines Downloaded from by guest on 16 September 2017 5. ..... SBP systolic blood pressure s.c. subcutaneous SGLT2 sodium-glucose co-transporter-2 SPECT single-photon emission computed tomography STEMI ST-segment elevation myocardial infarction STREAM STrategic Reperfusion Early After Myocardial infarction TIMI Thrombolysis In Myocardial Infarction TNK-tPA Tenecteplase tissue plasminogen activator TOTAL Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI tPA tissue plasminogen activator UFH unfractionated heparin VALIANT VALsartan In Acute myocardial iNfarcTion VF ventricular fibrillation VT ventricular tachycardia 24/7 24 h a day, seven days a week 1. Preamble Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strat- egies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions con- cerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate. A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other soci- eties and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (Guidelines/Clinical-Practice-Guidelines/Guidelines-development/ Writing-ESC-Guidelines). ESC Guidelines represent the official posi- tion of the ESC on a given topic and are regularly updated. Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a com- prehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic pro- cedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded accord- ing to predefined scales, as outlined in Tables 1 and 2. The experts of the writing and reviewing panels provided declara- tion of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http:// www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry. The ESC CPG supervises and coordinates the preparation of new ESC Guidelines. The Committee is also responsible for the endorse- ment process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating. Table 1 Classes of recommendations ESC Guidelines 5 Downloaded from by guest on 16 September 2017 6. ..... The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recom- mendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non- specialists and an electronic version for digital applications (smart- phones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and imple- ment all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations. Surveys and registries are needed to verify that real-life daily prac- tice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription. 2. Introduction Updates on the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) should be based on sound evidence, derived from well-conducted clinical trials whenever possi- ble, or motivated expert opinion when needed. It must be recognized that, even when excellent clinical trials have been undertaken, the results are open to interpretation and treatments may need to be adapted to take account of clinical circumstances and resources. The present Task Force has made an important effort to be as aligned as possible with the other ESC Guidelines1–6 and consensus documents, including the simultaneously published update on dual antiplatelet therapy (DAPT),7 for consistency in the ESC Guidelines strategy. The levels of evidence and the strengths of recommenda- tion of particular treatment options were weighed and graded according to pre-defined scales, as outlined in Tables 1 and 2. Despite recommendations with a level of evidence being based on expert opinion, this Task Force decided to add references to guide the reader regarding data that were taken into consideration for these decisions in some cases. 2.1 Definition of acute myocardial infarction The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial injury (defined as an elevation of car- diac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia.8 For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms sugges- tive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment ele- vation myocardial infarction (MI) (NSTEMI) and separate guidelines have recently been developed for these.2 Some patients with MI develop Q-waves (Q-wave MI), but many do not (non-Q-wave MI). In addition to these categories, MI is classified into various types, based on pathological, clinical, and prognostic differences, along with different treatment strategies (see the Third Universal Definition of MI document,8 which will be updated in 2018). Despite the fact that the majority of STEMI patients are classified as a type 1 MI (with evi- dence of a coronary thrombus), some STEMIs fall into other MI types.8 MI, even presenting as STEMI, also occurs in the absence of obstructive coronary artery disease (CAD) on angiography.9–12 This type of MI is termed 'myocardial infarction with non-obstructive cor- onary arteries' (MINOCA) and is discussed in Chapter 9 of this document. 2.2 Epidemiology of ST-segment elevation myocardial infarction Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. However, in Europe, there has been an overall trend for a reduction in ischaemic heart disease mortality over the past three decades.13 Ischaemic heart disease now accounts for almost 1.8 million annual deaths, or 20% of all deaths in Europe, although with large variations between countries.14 The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively.15,16 Probably the most comprehensive European STEMI registry is found in Sweden, where the incidence rate of STEMI was 58 per 100000 per year in 2015.17 In other European countries, the incidence rate ranged from 43 to 144 per 100000 per year.18 Similarly, the reported adjusted incidence rates from the USA decreased from 133 per 100000 in 1999 to 50 per 100000 in 2008, whereas the incidence of NSTEMI remained con- stant or increased slightly.19 There is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women.17,20 The mortality in STEMI patients is influenced by many factors, among them advanced age, Killip class, time delay to treatment, Table 2 Levels of evidence 6 ESC Guidelines Downloaded from by guest on 16 September 2017 7. ..... presence of emergency medical system (EMS)-based STEMI net- works, treatment strategy, history of MI, diabetes mellitus, renal fail- ure, number of diseased coronary arteries, and left ventricular ejection fraction (LVEF). Several recent studies have highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention.14,21,22 Nevertheless, mortality remains substantial; the in- hospital mortality of unselected patients with STEMI in the national registries of the ESC countries varies between 4 and 12%,23 while reported 1-year mortality among STEMI patients in angiography registries is approximately 10%.24,25 Although ischaemic heart disease develops on average 7–10years later in women compared with men, MI remains a leading cause of death in women. Acute coronary syndrome (ACS) occurs three to four times more often in men than in women below the age of 60years, but after the age of 75, women represent the majority of patients.26 Women tend to present more often with atypical symptoms, up to 30% in some registries,27 and tend to present later than men.28,29 It is therefore important to maintain a high degree of awareness for MI in women with potential symptoms of ischaemia. Women also have a higher risk of bleeding complications with PCI. There is an ongoing debate regarding whether outcomes are poorer in women, with several studies indicating that a poorer outcome is related to older age and more comorbidities among women suffering MI.26,30,31 Some studies have indicated that women tend to undergo fewer interventions than men and receive reperfusion therapy less fre- quently.26,32,33 These guidelines aim to highlight the fact that women and men receive equal benefit from a reperfusion strategy and STEMI- related therapy, and that both genders must be managed in a similar fashion. 3. What is new in the 2017 version? patients stenting Figure 1 What is new in 2017 STEMI Guidelines. BMS = bare metal stent; DES = drug eluting stent; IRA = infarct related artery; i.v. = intravenous; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SaO2 = arterial oxygen saturation; STEMI = ST-elevation myocardial infarction; TNK-tPA = Tenecteplase tissue plasminogen activator. For explanation of trial names, see list of. a Only for experienced radial operators. b Before hospital discharge (either immediate or staged). c Routine thrombus aspiration (bailout in certain cases may be considered). d In 2012 early discharge was considered after 72h, in 2017 early discharge is 48–72h. e If symptoms or haemodynamic instability IRA should be opened regardless time from symptoms onset. In left and mid panels, below each recommendation, the most representative trial (acronym and reference) driving the indication is mentioned. ESC Guidelines 7 Downloaded from by guest on 16 September 2017 8. ..... 4. Emergency care 4.1 Initial diagnosis Management—including diagnosis and treatment—of STEMI starts from the point of first medical contact (FMC, defined in Table 4). It is recommended that a regional reperfusion strategy should be estab- lished to maximize efficiency. A working diagnosis of STEMI (called the 'STEMI diagnosis' throughout this document) must first be made. This is usually based on symptoms consistent with myocardial ischaemia (i.e. persistent chest pain) and signs [i.e. 12-lead electrocardiogram (ECG)]. Important clues are a history of CAD and radiation of pain to the neck, lower jaw, or left arm. Some patients present with less-typical symptoms such as shortness of breath, nausea/vomiting, fatigue, pal- pitations, or syncope.34 A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not rec- ommended as a diagnostic manoeuvre.35 In cases of symptom relief after nitroglycerin administration, another 12-lead ECG must be obtained. A complete normalization of the ST-segment elevation after nitroglycerin administration, along with complete relief of symp- toms, is suggestive of coronary spasm, with or without associated MI. In these cases, an early coronary angiography (within 24h) is recom- mended. In cases of recurrent episodes of ST-segment elevation or chest pain, immediate angiography is required. It is recommended to initiate ECG monitoring as soon as possible in all patients with suspected STEMI in order to detect life- threatening arrhythmias and allow prompt defibrillation if indicated. When a STEMI is suspected, a 12-lead ECG must be acquired and interpreted as soon as possible at the time of FMC to facilitate early STEMI diagnosis and triage.36–40 In patients with a clinical suspicion of myocardial ischaemia and ST- segment elevation, reperfusion therapy needs to be initiated as soon as possible.41 If the ECG is equivocal or does not show evidence to support the clinical suspicion of MI, ECGs should be repeated and, when possible compared with previous recordings. If interpretation of pre-hospital ECG is not possible on-site, field transmission of the ECG is recommended.42 ECG criteria are based on changes of electrical currents of the heart (measured in millivolts). Standard calibration of the ECG is 10mm/mV. Therefore 0.1mV equals to 1 mm square on the vertical axis. For simplicity, in this document ECG deviations are expressed in mm following the standard calibration. In the proper clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation 2.5mm in men 40years, 2 mm in men 40years, or 1.5 mm in women in leads V2–V3 and/or 1 mm in the other leads [in the absence of left ventricular (LV) hypertrophy or left bundle branch block LBBB)].8 In patients with inferior MI, it is recommended to record right precordial leads (V3R and V4R) seek- ing ST-segment elevation, to identify concomitant right ventricular (RV) infarction.8,43 Likewise, ST-segment depression in leads V1–V3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation 0.5mm recorded in leads V7–V9 should be considered as a means to identify posterior MI.8 The presence of a Q-wave on the ECG should not necessarily change the reperfusion strategy decision. The ECG diagnosis may be more difficult in some cases, which nevertheless deserve prompt management and triage. Among these: Bundle branch block. In the presence of LBBB, the ECG diagno- sis of AMI is difficult but often possible if marked ST-segment abnor- malities are present. Somewhat complex algorithms have been offered to assist the diagnosis,50,51 but they do not provide diagnostic cer- tainty.52 The presence of concordant ST-segment elevation (i.e. in leads with positive QRS deflections) appears to be one of the best indi- cators of ongoing MI with an occluded infarct artery.53 Patients with a clinical suspicion of ongoing myocardial ischaemia and LBBB should be managed in a way similar to STEMI patients, regardless of whether the LBBB is previously known. It is important to remark that the presence of a (presumed) new LBBB does not predict an MI per se.54 Patients with MI and right bundle branch block (RBBB) have a poor prognosis.55 It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.55 Therefore, a primary PCI strat- egy (emergent coronary angiography and PCI if indicated) should be considered when persistent ischaemic symptoms occur in the pres- ence of RBBB. Recommendations for initial diagnosis Recommendations Classa Levelb ECG monitoring 12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.36,38 I B ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.44,45 I B The use of additional posterior chest wall leads (V7–V9) in patients with high suspicion of posterior MI (circumflex occlusion) should be considered.8,46–49 IIa B The use of additional right precordial leads (V3R and V4R) in patients with inferior MI should be considered to identify concomi- tant RV infarction.8,43 IIa B Blood sampling Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.8 I C ECG = electrocardiogram; FMC = first medical contact; MI = myocardial infarc- tion; RV = right ventricle; STEMI = ST-segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. 8 ESC Guidelines Downloaded from by guest on 16 September 2017 9. ..... Ventricular pacing. Pacemaker rhythm may also prevent interpretation of ST-segment changes and may require urgent angiog- raphy to confirm diagnosis and initiate therapy. Reprogramming the pacemaker—allowing an evaluation of ECG changes during intrinsic heart rhythm—may be considered in patients who are not depend- ent on ventricular pacing, without delaying invasive investigation.56,57 Non-diagnostic ECG. Some patients with an acute coronary occlusion may have an initial ECG without ST-segment elevation, sometimes because they are seen very early after symptom onset (in which case, one should look for hyper-acute T-waves, which may pre- cede ST-segment elevation). It is important to repeat the ECG or monitor for dynamic ST-segment changes. In addition, there is a con- cern that some patients with acute occlusion of a coronary artery and ongoing MI, such as those with an occluded circumflex coronary artery,58,59 acute occlusion of a vein graft, or left main disease, may present without ST-segment elevation and be denied reperfusion ther- apy, resulting in a larger infarction and worse outcomes. Extending the standard 12-lead ECG with V7–V9 leads may identify some of these patients. In any case, suspicion of ongoing myocardial ischaemia is an indication for a primary PCI strategy even in patients without diagnos- tic ST-segment elevation.8,38,46–49 Table 3 lists the atypical ECG pre- sentations that should prompt a primary PCI strategy in patients with ongoing symptoms consistent with myocardial ischaemia. Isolated posterior MI. In AMI of the inferior and basal portion of the heart, often corresponding to the left circumflex territory, isolated ST-segment depression 0.5mm in leads V1–V3 represents the dominant finding. These should be managed as a STEMI. The use of additional posterior chest wall leads [elevation V7–V9 0.5 mm (1 mm in men, 40 years old)] is recommended to detect ST- segment elevation consistent with inferior and basal MI. Left main coronary obstruction. The presence of ST depres- sion 1 mm in six or more surface leads (inferolateral ST depres- sion), coupled with ST-segment elevation in aVR and/or V1, suggests multivessel ischemia or left main coronary artery obstruction, partic- ularly if the patient presents with haemodynamic compromise.60 Blood sampling for serum markers is routinely carried out in the acute phase. This is indicated, but should not delay the reperfusion strategy/treatment. If in doubt regarding the possibility of acute evolving MI, emergency imaging aids the provision of timely reperfusion therapy to these patients. Recommendations for the use of echocardiography for ini- tial diagnosis are described in section 6.6.2. If echocardiography is not available or if doubts persist after echo, a primary PCI strategy is indi- cated (including immediate transfer to a PCI centre if the patient is being treated in a non-PCI centre). In the STEMI emergency setting, there is no role for routine com- puted tomography (CT). Use of CT should be confined to selected cases where acute aortic dissection or pulmonary embolism is sus- pected, but CT is not recommended if STEMI diagnosis is likely. Some non-AMI conditions can present with symptoms and ECG findings similar to STEMI. An emergency coronary angiography is therefore indicated in these cases (Chapter 9 expands on this topic). 4.2 Relief of pain, breathlessness, and anxiety Relief of pain is of paramount importance, not only for comfort rea- sons but because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. Titrated intravenous (i.v.) opioids (e.g. morphine) are the anal- gesics most commonly used in this context. However, morphine use is associated with a slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagre- lor, and prasugrel), which may lead to early treatment failure in sus- ceptible individuals.61–63 Table 3 Atypical electrocardiographic presentations that should prompt a primary percutaneous coronary intervention strategy in patients with ongoing symp- toms consistent with myocardial ischaemia ECG = electrocardiogram; LBBB = left bundle branch block; RBBB = right bundle branch block; RV = right ventricular; STEMI = ST-segment elevation myocardial infarction. Relief of hypoxaemia and symptoms Recommendations Classa Levelb Hypoxia Oxygen is indicated in patients with hypo- xaemia (SaO2 90% or PaO2 60 mmHg). I C Routine oxygen is not recommended in patients with SaO2 90%.64–66 III B Symptoms Titrated i.v. opioids should be considered to relieve pain. IIa C A mild tranquillizer (usually a benzodiaze- pine) should be considered in very anxious patients. IIa C i.v. = intravenous; PaO2 = partial pressure of oxygen; SaO2 = arterial oxygen saturation. a Class of recommendation. b Level of evidence. ESC Guidelines 9 Downloaded from by guest on 16 September 2017 10. ..... Oxygen is indicated in hypoxic patients with arterial oxygen satu- ration (SaO2) 90%. There is some evidence suggesting that hyper- oxia may be harmful in patients with uncomplicated MI, presumably due to increased myocardial injury.64–67 Thus, routine oxygen is not recommended when SaO2 is 90%. Anxiety is a natural response to the pain and the circumstances surrounding an MI. Reassurance of patients and those closely associ- ated with them is of great importance. A mild tranquillizer (usually a benzodiazepine) should be consid- ered in anxious patients. 4.3 Cardiac arrest Many deaths occur very early after

PCI-related delay in the range of 110–120 min, being in the range of the times identified in old studies and registries as the limit delay to choose PCI.107,117–120 If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytics within 10min from STEMI diagnosis. This time is selected based on the median time from randomization to bolus recorded in the STREAM trial, which was 9 min.121 In previous ESC STEMI guidelines,122 the target time was 30 min, but this was calcu- lated from FMC (as opposed to STEMI diagnosis). STEMI diagnosis should occur within 10min from FMC. Figure 3 summarizes target times for patients presenting in the pre- hospital setting or in a non-PCI centre. To shorten time to treatment, fibrinolysis should be administered in the pre-hospital setting if possible98,121,123 (Figures 2 and 3). Patients should be transferred to a PCI-capable facility as soon as pos- sible after bolus of lytics administration. Rescue PCI is indicated in the case of failed fibrinolysis (i.e. ST-segment resolution 50% within 60–90 min of fibrinolytic administration), or in the presence of hae- modynamic or electrical instability, worsening ischaemia, or persis- tent chest pain,121,124 while a routine early PCI strategy is indicated after successful fibrinolysis (preferably 2–24h after fibrinolysis) (see section 5.3).125–130 Patients with a clinical presentation compatible with AMI and a non-interpretable ST-segment on the ECG, such as those with bun- dle branch block or ventricular pacing,55,131,132 should undergo a pri- mary PCI strategy. There is general agreement that a primary PCI strategy should also be followed for patients with symptoms lasting 12h in the presence of: (1) ECG evidence of ongoing ischaemia; (2) ongoing or recurrent pain and dynamic ECG changes; and (3) ongoing or recurrent pain, symptoms, and signs of heart failure, shock, or malignant arrhythmias. However, there is no consensus as to whether PCI is also beneficial in patients presenting 12h from symptom onset in the absence of clinical and/or electrocardiographic evidence of ongoing ischaemia. In asymptomatic patients without persistent symptoms 12–48h after symptom onset, a small (n = 347) randomized study showed improved myocardial salvage and 4 year survival in patients treated with primary PCI compared with conservative treatment alone.133,134 However, in stable patients with persistent occlusion of the IRA 3–28 days after MI, the large (n = 2166) Occluded Artery Trial (OAT) revealed no clinical benefit from routine coronary interven- tion with medical management, beyond that from medical manage- ment alone.135,136 A meta-analysis of trials testing whether late recanalization of an occluded IRA is beneficial showed no benefit of reperfusion.137 Therefore, routine PCI of an occluded IRA in asymp- tomatic patients 48h after onset of symptoms is not indicated. These patients should be managed like all patients with chronic total occlusion, in which revascularization should be considered in the presence of symptoms or objective evidence of viability/ischaemia in the territory of the occluded artery.1 Recommendations for reperfusion therapy Recommendation Classa Levelb Reperfusion therapy is indicated in all patients with symptoms of ischaemia of _ 12 h duration and persistent ST-seg- ment elevation.119,138 I A A primary PCI strategy is recommended over fibrinolysis within indicated timeframes.114,116,139,140 I A If timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.107,120,122 I A In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symp- toms suggestive of MI and at least one of the following criteria present: - haemodynamic instability or cardiogenic shock - recurrent or ongoing chest pain refrac- tory to medical treatment - life-threatening arrhythmias or cardiac arrest - mechanical complications of MI - acute heart failure - recurrent dynamic ST-segment or T- wave changes, particularly with intermit- tent ST-segment elevation. I C Early angiography (within 24 h) is recom- mended if symptoms are completely relieved and ST-segment elevation is com- pletely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-seg- ment elevation). I C In patients with time from symptom onset 12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms sugges- tive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.141 I C A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset.133,134,142 IIa B In asymptomatic patients, routine PCI of an occluded IRA 48 h after onset of STEMI is not indicated.135,137 III A IRA = infarct-related artery; MI, myocardial infarction; PCI = percutaneous coro- nary intervention; STEMI = ST-segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. ESC Guidelines 15 Downloaded from by guest on 16 September 2017 16. ..... Table 5 summarizes the important time targets in acute STEMI. 5.2 Primary percutaneous coronary intervention and adjunctive therapy 5.2.1 Procedural aspects of primary percutaneous coronary intervention 5.2.1.1 Access route Over recent years, several studies have provided robust evidence in favour of the radial approach as the default access site in ACS patients undergoing primary PCI by experienced radial operators. The Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX)143 trial recruited 8404 ACS patients (48% STEMI) who were randomly allocated to transradial or transfemoral access. Radial access was associated with lower risks of access site bleeding, vascular complications, and need for transfusion. Importantly, there was a significant mortality benefit in patients allocated to the transradial access site, which reinforced previous observations from the Radial Versus Femoral Access for Coronary Intervention (RIVAL) access for coronary intervention trial,144 and the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial.145 No significant interaction was observed in the MATRIX trial between the type of ACS and treatment benefit, suggesting that the results of this investigation can be extended with confidence to the treatment of patients with STEMI. 5.2.1.2 Stenting in primary percutaneous intervention Coronary stenting is the technique of choice during primary PCI. Compared with balloon angioplasty alone, stenting with a bare-metal stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularization but is not associated with a reduction in the mortality rate.146,147 In primary PCI, drug-eluting stents (DES) reduce the risk of repeated target vessel revascularization compared with BMS.148 New-generation DES have shown superior safety and preserved or even improved efficacy compared with first-generation DES, in particular with respect to lower risks of stent thrombosis and recur- rent MI. In two recent trials—the Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with AMI (COMFORTABLE AMI) trial149 and the Everolimus-Eluting Stents Versus Bare-Metal Stents in ST- Segment Elevation Myocardial Infarction (EXAMINATION) trial150 —new-generation DES have been shown to be superior to BMS in patients with AMI, mostly in terms of need for reintervention. In the latter trial, the recently released 5 year follow-up results showed a reduction in all-cause mortality by DES as compared to BMS.151 In the Norwegian Coronary Stent (NORSTENT) trial,152 9013 patients undergoing PCI (26% with STEMI) were randomized to DES or BMS. There were no differences in the incidence of the pri- mary endpoint (composite of death from any cause or non-fatal spontaneous MI) after a median follow-up of 5 years. However, DES were associated with lower rates of definite stent thrombosis (0.8% vs. 1.2%; P = 0.0498) and of target lesion and any repeat revascula- tion (16.5% vs. 19.8%; P 0.001).152 Deferring stenting in primary PCI has been investigated as an option to reduce microvascular obstruction (MVO) and preserve microcirculatory function. Two small studies recently found opposite results in the effect of deferred stenting on cardiac magnetic reso- nance (CMR) imaging-measured MVO.153,154 In the larger DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarc- tion (DANAMI 3-DEFER) trial,155 in 1215 STEMI patients, deferred stenting (48 h after the index procedure) had no effect on the pri- mary clinical outcome (composite of all-cause mortality, non-fatal MI, or ischaemia-driven revascularization of non-IRA lesions). Routine deferred stenting was associated with a higher need for target vessel revascularization. Based on these findings, routine use of deferred stenting is not recommended. 5.2.1.3 Thrombus aspiration A number of small-scale or single-centre studies and one meta-analysis of 11 small trials156 suggested that there could be benefits from routine manual thrombus aspiration during primary PCI. Recently, two large (10000 and 7000 patients) randomized controlled trials, which were adequately powered to detect superiority of routine manual thrombus aspiration versus conventional PCI, showed no benefit on clinical outcomes of routine aspiration strategy overall.157–160 A safety concern emerged in the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) trial (n = 10732), with an increase in the risk of stroke.161 In the subgroup with high thrombus burden [TIMI (Thrombolysis in Myocardial Infarction) thrombus grade 3], thrombus aspiration was associated with fewer cardiovascular deaths [170 (2.5%) vs. 205 (3.1%); hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.65–0.98; P = 0.03] and with more strokes or transient ischaemic attacks [55 (0.9%) vs. 34 (0.5%); odds Table 5 Summary of important time targets ECG = electrocardiogram; FMC = first medical contact; PCI = percutaneous cor- onary intervention; STEMI = ST-segment elevation myocardial infarction a ECG should be interpreted immediately. 16 ESC Guidelines Downloaded from by guest on 16 September 2017 17. ..... ratio 1.56, 95% CI 1.02–2.42, P =0.04]. However, the interaction P val- ues were 0.32 and 0.34, respectively.162 In the Taste157 and TOTAL trials159 , 1–5% of randomized patients crossed over from PCI alone to thrombus aspiration. Based on these data and the results of a recent meta-analysis,162 routine thrombus aspiration is not recommended, but in cases of large residual throm- bus burden after opening the vessel with a guide wire or a balloon, thrombus aspiration may be considered. 5.2.1.4 Multivessel coronary revascularization Multivessel disease is common (in approximately 50%) in patients with STEMI.163,164 While it is recommended to always treat the IRA, evidence supporting immediate (preventive) revascularization of additional significant coronary stenoses is conflicting. It has been reported that patients with extensive CAD in vessels remote from the IRA have lower rates of ST-segment recovery and an adverse prognosis following primary PCI.163 Data from the US National Cardiovascular Data Registry and New York State's Percutaneous Coronary Interventions Reporting System suggested an increase in adverse events, including mortality, in patients treated with immedi- ate multivessel revascularization versus IRA PCI only, while patients in cardiogenic shock were excluded from the analysis.165,166 Randomized clinical trials addressing this issue have been small (each of them included from 69 to 885 patients). One study allocated 214 STEMI patients with multivessel disease to three arms: IRA angioplasty- only, simultaneous treatment of non-IRA lesions, and staged revascula- rization of the non-IRA. At a mean follow-up of 2.5years, patients allo- cated to IRA angioplasty-only had more major adverse cardiac events (MACE) (i.e. death, reinfarction, rehospitalization for ACS, and repeat coronary revascularization) than the patients treated with other strat- egies.167 After this study, four randomized clinical trials have compared PCI of the IRA only vs. complete revascularization: the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial (n = 465, 23months follow-up),168 the Complete Versus Lesion-Only Primary PCI Trial (CvLPRIT) (n = 296, 12months follow-up),169 the Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel dis- ease (DANAMI-3–PRIMULTI) trial (n = 627, 27months follow-up),170 and the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel dis- ease (Compare-Acute, n = 885, 12months follow-up) trial.171 PCI of non-IRA was done either during the index procedure (PRAMI and Compare-Acute), staged during hospital admission (DANAMI- 3–PRIMULTI), or any time before discharge (immediate or staged) (CVLPRIT). Indication for PCI in non-IRA was angiography-guided in lesions with 50% stenosis (PRAMI), 70% stenosis (CVLPRIT), or fractional flow reserve (FFR)-guided (DANAMI-3–PRIMULTI and Compare-Acute). Primary outcome (composite of different end- points) was significantly reduced in the complete revascularization group in all four trials. Total mortality was not statistically different in any of the four trials. Repeat revascularization was significantly reduced in the complete revascularization arm in the PRAMI, DANAMI- 3–PRIMULTI, and Compare-Acute trials. Non-fatal MI was reduced in the non-IRA PCI group only in PRAMI. The lack of significant treatment effect of non-IRA lesion intervention on death or MI was confirmed by three meta-analyses172–174 (none of these meta-analyses included the Compare-Acute trial, and one173 did not include the DANAMI-3–PRIMULTI). Based on these data, revascularization of non-IRA lesions should be considered in STEMI patients with multives- sel disease before hospital discharge. As the optimal timing of revascu- larization (immediate vs. staged) has not been adequately investigated, no recommendation in favour of immediate vs. staged multivessel PCI can be formulated. 5.2.1.5 Intra-aortic balloon pump The Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocar- dial Infarction (CRISP AMI) trial showed no benefit from a routine intra-aortic balloon pump (IABP) in anterior MI without shock,175 but there was increased bleeding, which is consistent with previous data regarding the role of IABP in high-risk STEMI without cardiogenic shock.176 In addition, a recent randomized trial showed that IABP did not improve outcomes in MI with cardiogenic shock.177 Haemody- namic support in patients with cardiogenic shock is discussed in Chapter 8. Procedural aspects of the primary percutaneous cor- onary intervention strategy Recommendations Classa Levelb IRA strategy Primary PCI of the IRA is indicated.114,116,139,140 I A New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI. I C IRA technique Stenting is recommended (over balloon angio- plasty) for primary PCI.146,147 I A Stenting with new-generation DES is recom- mended over BMS for primary PCI.148–151,178,179 I A Radial access is recommended over femoral access if performed by an experienced radial operator.143–145,180 I A Routine use of thrombus aspiration is not recommended.157,159 III A Routine use of deferred stenting is not recommended.153–155 III B Non-IRA strategy Routine revascularization of non-IRA lesions should be considered in STEMI patients with mul- tivessel disease before hospital discharge.167–173 IIa A Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock. IIa C CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed. IIa C CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST- segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. ESC Guidelines 17 Downloaded from by guest on 16 September 2017 18. ..... 5.2.2 Periprocedural pharmacotherapy 5.2.2.1 Platelet inhibition Patients undergoing primary PCI should receive DAPT, a combina- tion of aspirin and a P2Y12 inhibitor, and a parenteral anticoagulant. Aspirin can be given orally including chewing, or i.v. to ensure com- plete inhibition of thromboxane A2-dependent platelet aggregation. The oral dose of plain aspirin (non-enteric-coated formulation) should preferably be 150–300 mg. There are few clinical data on the optimal i.v. dosage. Given a 50% oral bioavailability of oral aspirin, a corresponding dose is 75–150mg. Pharmacological data suggest that this lower dose range avoids inhibition of cyclooxygenase-2- dependent prostacyclin. A recent randomized study showed that a single dose of 250 or 500 mg acetylsalicylic acid i.v. compared to 300 mg orally was associated with a faster and more complete inhibi- tion of thromboxane generation and platelet aggregation at 5 min, with comparable rates of bleeding complications.181 There is limited evidence with respect to when the P2Y12 inhibitor should be initiated in STEMI patients. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial182 is the only randomized study testing the safety and efficacy of different timings of P2Y12 inhibitor initiation in STEMI. In this trial, patients were randomized to receive ticagrelor either during transfer to a primary PCI centre or immediately before angiography.182 The median difference between the two tested loading treatment strat- egies was only 31min. This study failed to meet the pre-specified pri- mary endpoint in terms of improved ST-segment elevation resolution or TIMI flow before intervention. Rates of major and minor bleeding events were identical in both treatment arms. While the evidence of a clinical benefit of P2Y12 inhibitor pre-treatment in this setting is lacking, early initiation of a P2Y12 inhibitor while the patient is being transported to a primary PCI centre is common prac- tice in Europe and is consistent with the pharmacokinetic data. Furthermore, early treatment with high-dose clopidogrel was supe- rior to in-catheterization laboratory treatment in observational stud- ies and one small randomized trial.183–185 In all, the data suggest that the earliest administration may be preferable to achieve early efficacy, particularly for long delays. However, in cases in which the STEMI diagnosis is not clear, delaying P2Y12 inhibitor loading until the anat- omy is known should be considered. The preferred P2Y12 inhibitors are prasugrel [60 mg loading dose and 10mg maintenance dose once daily per os (p.o.)] or ticagrelor (180 mg p.o. loading dose and 90 mg maintenance dose twice daily). These drugs have a more rapid onset of action, greater potency, and are superior to clopidogrel in clinical outcomes.186,187 Prasugrel is contraindicated in patients with previous stroke/transient ischaemic attack, and its use is generally not recommended in patients aged 75years or in patients with lower body weight (60kg) as it was not associated with net clinical benefit in these subsets. In case prasu- grel is used in these patients, a reduced dose (5mg)188 is recom- mended. Ticagrelor may cause transient dyspnoea at the onset of therapy, which is not associated with morphological or functional lung abnormalities, and which rarely leads to permanent discontinua- tion.189 Neither prasugrel nor ticagrelor should be used in patients with a previous haemorrhagic stroke, in patients on oral anticoagu- lants, or in patients with moderate-to-severe liver disease. When neither of these agents is available (or if they are contraindi- cated), clopidogrel 600mg p.o. should be given instead.190 Clopidogrel has not been evaluated against placebo in any large out- comes studies in the setting of primary PCI, but a higher regimen of a 600mg loading dose/150 mg maintenance dose in the first week was superior to the 300/75 mg regimen in the subset of patients under- going PCI in the Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events–Seventh organization to assess strategies in ischaemic syndromes (CURRENT-OASIS 7) trial,190 and use of high clopidogrel loading doses has been demonstrated to achieve more rapid inhibition of the adenosine diphosphate receptor. All P2Y12 inhibitors should be used with caution in patients at high risk of bleed- ing or with significant anaemia. Cangrelor is a potent i.v. reversible P2Y12 inhibitor with a rapid onset and offset of action. It has been assessed in three random- ized controlled trials enrolling patients with PCI for stable angina or ACS against clopidogrel loading or placebo.191–193 A pooled analysis of these three trials showed that cangrelor reduced peri- procedural ischaemic complications at the expense of an increased risk of bleeding.194 The fact that no potent P2Y12 inhibitors (prasu- grel or ticagrelor) were used in patients with an ACS, and only about 18% of the enrolled patients presented with STEMI,193 limits the applicability of the results to current practice of management of STEMI patients. Nevertheless, cangrelor may be considered in patients not pre-treated with oral P2Y12 receptor inhibitors at the time of PCI or in those who are considered unable to absorb oral agents. The pre-hospital routine upstream use of glycoprotein (GP) IIb/IIIa inhibitors before primary PCI has not been demonstrated to offer a benefit and increases bleeding risk compared with routine use in the catheterization laboratory.195,196 Procedural use of abciximab plus unfractionated heparin (UFH) showed no benefit compared to biva- lirudin.197 Using GP IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of a large thrombus, slow- or no-reflow, and other thrombotic complications is reasonable, although this strategy has not been tested in a randomized trial. Overall, there is no evi- dence to recommend the routine use of GP IIb/IIIa inhibitors for pri- mary PCI. The intracoronary administration of GP IIb/IIIa inhibitors is not superior to its i.v. use.198 5.2.2.2 Anticoagulation Anticoagulant options for primary PCI include UFH, enoxaparin, and bivalirudin. Use of fondaparinux in the context of primary PCI was associated with potential harm in the Organization for the Assessment of Strategies for Ischemic Syndromes 6 (OASIS 6) trial and is not recommended.199 There has been no placebo-controlled trial evaluating UFH in pri- mary PCI, but there is a large body of experience with this agent. 18 ESC Guidelines Downloaded from by guest on 16 September 2017 19. Dosage should follow standard recommendations for PCI (i.e. initial bolus 70–100U/kg). There are no robust data recommending the use of activated clotting time to tailor dose or monitor UFH, and if activated clotting time is used, it should not delay recanalization of the IRA. An i.v. bolus of enoxaparin 0.5mg/kg was compared with UFH in the randomized open-label Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up (ATOLL) trial, including 910 STEMI patients.200 The primary composite endpoint of 30 day death, MI, procedural failure, or major bleeding was not significantly reduced by enoxaparin (17% relative risk reduction, P = 0.063), but there was a reduction in the composite main secondary endpoint of death, recur- rent MI or ACS, or urgent revascularization. Importantly, there was no evidence of increased bleeding following the use of enoxaparin over UFH.200 In the per-protocol analysis of the ATOLL trial (87% of the study population), i.v. enoxaparin was superior to UFH in reduc- ing the primary endpoint, ischaemic endpoints, mortality, and major bleeding.201 In a meta-analysis of 23 PCI trials (30 966 patients, 33% primary PCI), enoxaparin was associated with a significant reduction in death compared to UHF. This effect was particularly significant in the primary PCI context and was associated with a reduction in major bleeding.202 Based on these considerations, enoxaparin should be considered in STEMI. Five dedicated randomized controlled trials have compared bivalir- udin with UFH with or without planned use of GP IIb/IIIa inhibitors in patients with STEMI.197,203–207 A meta-analysis of these trials showed no mortality advantage with bivalirudin and a reduction in the risk of major bleeding, but at the cost of an increased risk of acute stent thrombosis.208 In the recent MATRIX trial including 7213 ACS patients (56% with STEMI), bivalirudin did not reduce the incidence of the primary endpoint (composite of death, MI, or stroke) com- pared to UFH. Bivalirudin was associated with lower total and cardio- vascular mortality, lower bleeding, and more definite stent thrombosis.209 The recently published STEMI subanalysis confirmed a lack of statistical interaction between the type of ACS and out- comes within the study.210 The MATRIX trial showed that prolonging bivalirudin infusion after PCI did not improve the outcomes com- pared with bivalirudin infusion confined to the duration of PCI.209 However, a post hoc analysis suggested that prolonging bivalirudin with a full-PCI dose after PCI was associated with the lowest risk of ischaemic and bleeding events, which is in accordance with the cur- rent label of the drug.209 Based on these data, bivalirudin should be considered in STEMI, especially in patients at high bleeding risk.197,211,212 Bivalirudin is recommended for patients with heparin- induced thrombocytopenia. Routine post-procedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation [due, for instance, to atrial fibrillation (AF), mechanical valves, or LV thrombus)2 or prophylactic doses for the prevention of venous thromboembolism in patients requiring prolonged bed rest. Periprocedural and post-procedural antithrombotic therapya in patients undergoing primary percutaneous coronary intervention Recommendations Classb Levelc Antiplatelet therapy A potent P2Y12 inhibitor (prasugrel or tica- grelor), or clopidogrel if these are not avail- able or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindica- tions such as excessive risk of bleeding.186,187 I A Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications.213,214 I B GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication. IIa C Cangrelor may be considered in patients who have not received P2Y12 receptor inhibitors.192–194 IIb A Anticoagulant therapy Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI. I C Routine use of UFH is recommended. I C In patients with heparin-induced thrombo- cytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI. I C Routine use of enoxaparin i.v. should be considered.200–202 IIa A Routine use of bivalirudin should be considered.209,215 IIa A Fondaparinux is not recommended for pri- mary PCI.199 III B GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; UFH = unfractionated heparin. a Dose regimens are specified in Table 6. b Class of recommendation. c Level of evidence. ESC Guidelines 19 Downloaded from by guest on 16 September 2017 20. ..... 5.2.2.3 Therapies to reduce infarct size and microvascular obstruction Final infarct size and MVO are major independent predictors of long-term mortality and heart failure in survivors of STEMI.216,217 MVO is defined as inadequate myocardial perfusion after success- ful mechanical opening of the IRA, and is caused by several fac- tors.218 MVO is diagnosed immediately after PCI when post- procedural angiographic TIMI flow is 3, or in the case of a TIMI flow of 3 when myocardial blush grade is 0 or 1, or when ST reso- lution within 60–90 min of the procedure is 70%. Other non- invasive techniques to diagnose MVO are late gadolinium enhancement (LGE) CMR (the current state of the art for MVO identification and quantification), contrast echocardiography, single-photon emission computed tomography (SPECT), and posi- tron emission tomography (PET).218 Different strategies, such as coronary post-conditioning, remote ischaemic conditioning, early i.v. metoprolol, GP IIb/IIIa inhibitors, drugs targeting mitochondrial integrity or nitric oxide pathways, adenosine, glucose modulators, hypothermia, and others, have been shown to be beneficial in pre- clinical and small-scale clinical trials,217,219 but still there is no ther- apy aimed at reducing ischaemia/reperfusion injury (MI size) that is clearly associated with improved clinical outcomes. The reduction of ischaemia/reperfusion injury in general, and MVO in particular, remains an unmet need to further improve long-term ventricular function in STEMI. 5.3 Fibrinolysis and pharmacoinvasive strategy 5.3.1 Benefit and indication of fibrinolysis Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner, and pre- vents 30 early deaths per 1000 patients treated within 6 h after symptom onset.220 The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered 2 h after symptom onset.138,221 Fibrinolytic therapy is recommended within 12 h of symptom onset if primary PCI can- not be performed within 120 min from STEMI diagnosis (see Figure 3) and there are no contraindications. The later the patient presents (particularly after 3 h),98,120,121 the more consideration should be given to transfer for primary PCI (as opposed to admin- istering fibrinolytic therapy) because the efficacy and clinical bene- fit of fibrinolysis decrease as the time from symptom onset increases.120 In the presence of contraindications for fibrinolytic treatment, it is important to weigh the potentially life-saving effect of fibrinolysis against potentially life-threatening side effects, taking into account alternative treatment options such as delayed primary PCI. Table 6 Doses of antiplatelet and anticoagulant cotherapies in patients undergoing primary percutane- ous coronary intervention or not reperfused b.i.d. = twice a day; GP = glycoprotein; i.v. = intravenous; IU = international units; PCI = percutaneous coronary intervention; UFH = unfractionated heparin. 20 ESC Guidelines Downloaded from by guest on 16 September 2017 21. ..... Doses of fibrinolytic agents and antithrombotic co-therapies are listed in Table 7. 5.3.2 Pre-hospital fibrinolysis In a meta-analysis of six randomized trials (n = 6434), pre-hospital fibrinolysis reduced early mortality by 17% compared with in-hospital fibrinolysis,123 particularly when administered in the first 2 h of symp- tom onset.138 These and more recent data support pre-hospital initiation of fibrinolytic treatment when a reperfusion strategy is indi- cated.97,99,100,237 The STREAM trial showed that pre-hospital fibrinol- ysis followed by an early PCI strategy was associated with a similar outcome as transfer for primary PCI in STEMI patients presenting within 3 h after symptom onset who could not undergo primary PCI within 1 h after FMC.121,238 If trained medical or paramedical staff are able to analyse the ECG on- site or to transmit the ECG to the hospital for interpretation, it is Fibrinolytic therapy Recommendations Classa Levelb When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.96,98,123,222 I A A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.223,224 I B A half-dose of tenecteplase should be considered in patients 75 years of age.121 IIa B Antiplatelet co-therapy with fibrinolysis Oral or i.v. aspirin is indicated.213 I B Clopidogrel is indicated in addition to aspirin.225,226 I A DAPT (in the form of aspirin plus a P2Y12 inhibitorc) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI. I C Anticoagulation co-therapy with fibrinolysis Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days.199,224,227–233 The anticoagulant can be: • Enoxaparin i.v. followed by s.c. (preferred over UFH).227–232 • UFH given as a weight-adjusted i.v. bolus followed by infusion.224 • In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.199,233 I A I A I B IIa B Transfer after fibrinolysis Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.121,124,126–130,234 I A Interventions following fibrinolysis Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.124, 235 I A Rescue PCI is indicated immediately when fibrinolysis has failed (50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.121,124,236 I A Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.125–128,234 I A Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.124 I B DAPT = dual antiplatelet therapy; IRA = infarct-related artery; i.v. = intravenous; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; s.c. = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin. a Class of recommendation. b Level of evidence. c Clopidogrel is the P2Y12 inhibitor of choice as co-adjuvant and after fibrinolysis, but 48 h after fibrinolysis, switch to prasugrel/ticagrelor may be considered in patients who underwent PCI. ESC Guidelines 21 Downloaded from by guest on 16 September 2017 22. .....recommended to initiate fibrinolytic therapy in the pre-hospital setting. The aim is to start fibrinolytic therapy within 10min from STEMI diagnosis. 5.3.3 Angiography and percutaneous coronary intervention after fibrinolysis (pharmacoinvasive strategy) Following initiation of lytic therapy, it is recommended to transfer the patients to a PCI centre (Figure 3). In cases of failed fibrinolysis, or if there is evidence of reocclusion or reinfarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI is indi- cated.124 In this setting, re-administration of fibrinolysis has not been shown to be beneficial and should be discouraged.124 Even if it is likely that fibrinolysis will be successful (ST-segment resolution 50% at 60–90min; typical reperfusion arrhythmia; and disappear- ance of chest pain), a strategy of routine early angiography is recom- mended if there are no contraindications. Several randomized trials126–128,234,239,240 and meta-analyses129,130 have shown that early routine angiography with subsequent PCI (if needed) after fibrinolysis reduced the rates of reinfarction and recurrent ischaemia compared with a 'watchful waiting' strategy, in which angiography and revascularization were indicated only in patients with spontane- ous or induced severe ischaemia or LV dysfunction, or in those with a positive outpatient ischaemia test. The benefits of early routine PCI after fibrinolysis were seen in the absence of an increased risk of adverse events (stroke or major bleeding), and across patient sub- groups.241 Thus, early angiography with subsequent PCI if indicated is also the recommended standard of care after successful fibrinolysis (see Figure 3). A crucial issue is the optimal time delay between successful lysis and PCI; there was a wide variation in delay in trials, from a median of 1.3h in the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction (CAPITAL AMI) trial240 to 17h in the Grupo de Analisis de la Cardiopatıa Isque´mica Aguda (GRACIA)-1234 and STREAM trials.121 In a pooled patient-level analysis of six randomized trials, very early angiography (2h) after fibrinolysis was not associated with an increased risk of 30day death/ reinfarction or in-hospital major bleeding, and a shorter time from symptom onset to angiography (4h) was associated with reduced 30day and 1year death/reinfarction and 30day recurrent ischaemia.125 Table 7 Doses of fibrinolytic agents and antithrombotic co-therapies a PTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; i.v. = intravenous; IU = international units; rPA = recombinant plasminogen activator; s.c. = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin. 22 ESC Guidelines Downloaded from by guest on 16 September 2017 23. ..... Based on this analysis, as well as on trials having a median delay between start of lysis and angiography of 2–17h,121,126–128 a time- window of 2–24h after successful lysis is recommended. 5.3.4 Comparison of fibrinolytic agents A fibrin-specific agent should be preferred.224 Single-bolus weight- adjusted tenecteplase tissue plasminogen activator (TNK-tPA) is equivalent to accelerated tPA in reducing 30 day mortality, but is safer in preventing non-cerebral bleeds and blood transfusion, and is easier to use in the pre-hospital setting.223 5.3.5 Adjunctive antiplatelet and anticoagulant therapies An early study showed that the benefits of aspirin and fibrinolytics (i.e. streptokinase) were additive.213 The first dose of aspirin should be chewed or given i.v. and a low dose (75–100mg) given orally daily thereafter. Clopidogrel added to aspirin reduces the risk of cardio- vascular events and overall mortality in patients treated with fibrinol- ysis225,226 and should be added to aspirin as an adjunct to lytic therapy. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis. There is no evidence that administration of GP IIb/IIIa inhibitors improves myocardial perfusion or outcomes in patients treated with fibrinolysis, and bleeding may increase.242 Parenteral anticoagulation should preferably be given until revascula- rization (if performed). Otherwise, it should be given for at least 48h or for the duration of hospital stay, up to 8 days. In spite of an increased risk of major bleeding, the net clinical benefit favoured enoxaparin over UFH in the ASsessment of the Safety and Efficacy of a New Thrombolytic 3 (ASSENT 3) trial (n = 6095).227 In the large Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction 25 (ExTRACT–TIMI 25) trial (n = 20506), a lower dose of enoxaparin was given to patients 75years of age and to those with impaired renal function (estimated creatinine clearance 30mL/min). Enoxaparin was associated with a reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted UFH dose, but at the cost of a significant increase in non-cerebral bleeding complications. The net clinical benefit (i.e. absence of death, non-fatal infarction, and intracra- nial haemorrhage) favoured enoxaparin.229,230 Finally, fondaparinux was shown in the large OASIS-6 trial to be superior in this setting to placebo or UFH in preventing death and reinfarction,199,233 especially in patients who received streptokinase. In a large trial with streptokinase,243 significantly fewer reinfarc- tions were seen with bivalirudin given for 48 h compared with UFH, though at the cost of a modest and non-significant increase in non- cerebral bleeding complications. Bivalirudin has not been studied with fibrin-specific agents. Thus, there is no evidence in support of direct thrombin inhibitors as an adjunct to fibrinolysis. Weight-adjusted i.v. tenecteplase, aspirin, and clopidogrel given orally, and enoxaparin i.v. followed by s.c. administration until the time of PCI (revascularisation), comprise the antithrombotic cocktail most extensively studied as part of a pharmacoinvasive strategy.121,126,128,242,244 5.3.6 Hazards of fibrinolysis Fibrinolytic therapy is associated with a small but significant excess of strokes, largely attributable to cerebral haemorrhage, with the excess hazard appearing on the first day after treatment.220 Advanced age, lower weight, female sex, previous cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.245 In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.121,223,246 In the STREAM trial, the initial excess in intracranial haemorrhage in patients 75years was reduced after the protocol amendment to reduce the dose of tenecteplase by 50%. Data from a number of studies suggest that major non-cerebral bleeds occurred in 4–13% of the patients treated.121,223,224,246 Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Re- administration of streptokinase should be avoided because of antibodies that can impair its activity, and because of the risk of allergic reactions. 5.3.7 Contraindications to fibrinolytic therapy Short successful resuscitation does not contraindicate fibrinolytic therapy. In patients in refractory cardiac arrest, lytic therapy is not effective, increases the risk of bleeding, and is therefore not recom- mended. Prolonged, or traumatic but successful, resuscitation increases bleeding risk and is a relative contraindication to fibrinoly- sis.247 Table 8 lists the absolute and relative contraindications to fibri- nolytic therapy. Table 8 Contra-indications to fibrinolytic therapy DBP = diastolic blood pressure; SBP = systolic blood pressure. ESC Guidelines 23 Downloaded from by guest on 16 September 2017 24. ..... 5.4 Co

control Current guidelines on prevention recommend: (i) a diet similar to the Mediterranean diet, which includes a maximum of 10% of total energy intake from saturated fat, by replacing it with polyunsaturated fatty acids and as little as possible of trans fatty acids; (ii) salt intake of 5 g per day; (iii) 30–45g fibre per day; (iv) 200 g fruits and 200g vegetables per day; (v) fish 1–2 times per week (especially oily vari- eties); (vi) 30g unsalted nuts daily; (vii) limited alcohol intake [maxi- mum of 2 glasses (20 g of alcohol) daily for men and 1 for women]; and (viii) discouraging sugar-sweetened drinks.4 Moderate alcohol consumption in abstainers is not recommended. Overweight and obesity [body mass index (BMI) 25kg/m2] is associated with higher all-cause mortality compared with a healthy weight (BMI between 20 kg/m2 and 25kg/m2). Abdominal fat is par- ticularly harmful and weight loss has beneficial effects on cardiovascu- lar disease risk factors. Consequently, maintaining a healthy weight or losing weight is recommended for all subjects,308 including patients with STEMI. However, it has not been established that weight reduc- tion per se reduces mortality. 7.1.3 Exercise-based cardiac rehabilitation All AMI patients should participate in an exercise-based cardiac reha- bilitation programme,309 taking into account their age, pre-infarction level of activity, and physical limitations. A cardiac rehabilitation pro- gramme preferably includes exercise training, risk factor modification, education, stress management, and psychological support.309 In a large meta-analysis, exercise training as part of a cardiac rehabilitation pro- gramme was associated with a 22% reduction in cardiac mortality rate in patients with CAD.309 The benefit of cardiac rehabilitation appears to be through direct physiological effects of exercise training and through cardiac rehabilitation effects on risk factor control, lifestyle behaviours, and mood.310 An additional benefit in the context of a short hospital stay is to ensure proper titration and monitoring of key, evidence-based therapies after STEMI. Nowadays, most rehabilitation is offered as an outpatient programme of 8–24weeks' duration.311,312 7.1.4 Resumption of activities Return to work after AMI represents an important indicator of recovery. Younger women in particular are at greater risk of not returning to work, given evidence of their worse recovery after MI than similarly aged men.313 Decisions should be individualized, based on LV function, completeness of revascularization and rhythm con- trol, and the job characteristics. Extended sick leave is usually not beneficial and light-to-moderate physical activity after discharge should be encouraged. Sexual activity can be resumed early if adjusted to physical ability. Guidance on air travel including repatriation for patients suffering an MI abroad is constrained by limited data. Factors related to the clinical circumstances as well as length of travel, whether accompa- nied, and the degree of anxiety also play a role. For uncomplicated completely revascularized MI with LVEF 40% the risk is low and travelling is regarded as safe after hospital discharge (from day 3 onwards). In complicated STEMI, including patients with heart failure, LVEF 40%, residual ischaemia, and arrhythmia, travelling should be deferred until the condition is stable.314 7.1.5 Blood pressure control Hypertension is a prevalent risk factor in patients admitted with STEMI and, consequently, blood pressure should be well controlled. In addition to lifestyle changes, including reduced salt intake, increased physical activity, and weight loss, pharmacotherapy with a systolic blood pressure (SBP) target of 140 mmHg should be initi- ated. In elderly, frail patients, the target can be more lenient, whereas in patients at very high risk who tolerate multiple blood pressure- lowering drugs, a target of 120mmHg may be considered.4,315,316 Despite the proven efficacy of this treatment, non-adherence to life- style interventions and medications may affect treatment effect. 7.1.6 Adherence to treatment Low treatment adherence is an important barrier to achieving opti- mal treatment targets and is associated with worse outcomes.317 Delayed outpatient follow-up after AMI results in worse short- and long-term medication adherence.318 In a meta-analysis of 376 162 30 ESC Guidelines Downloaded from by guest on 16 September 2017 31.
..... patients, adherence to cardiovascular medications was estimated to be about 57% after a median of 2 years.319 It is generally recognized that adherence is determined by the interplay of socioeconomic, medication-related, condition-related, health system-related, and patient-related factors.320 A strategy to reduce poor adherence is the use of a fixed-dose combination or pol- ypill, including key medications to reduce cardiovascular risk, as a once-daily dose pill.321,322 The only study dedicated to post-MI patients is the recent phase 2 Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial,323 in which 695 patients post-MI were randomized to usual care or to a polypill- based strategy [polypill containing aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin]. In this trial, after 9 months of follow-up, the polypill group showed improved adherence compared with the group receiving separate medications. Larger trials are needed to confirm a clinical benefit in secondary prevention. Although low adherence has been qualified as an ubiquitous prob- lem,324 healthcare professionals and patients should be aware of this challenge and optimize communication by providing clear informa- tion, simplify treatment regimens, aim at shared decision-making, and implement repetitive monitoring and feedback. 7.2 Antithrombotic therapy Full text about long-term antithrombotic therapy can be found in the online Web Addenda. In addition, this topic is covered in great detail in the ESC Focused Update on DAPT in CAD published simultane- ously with these guidelines.7 7.2.1 Aspirin Aspirin is recommended indefinitely in all patients with STEMI.329,330 For long-term prevention, low aspirin doses (75–100 mg) are indi- cated due to similar anti-ischaemic and less adverse events than higher doses, as demonstrated in the CURRENT-OASIS 7 trial.330 7.2.2 Duration of dual antiplatelet therapy and antithrombotic combination therapies DAPT, combining aspirin and a P2Y12 inhibitor (i.e. prasugrel, ticagre- lor, or clopidogrel), is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months).186,187 Clopidogrel is recommended for 1 month in patients treated with fibrinolysis with- out subsequent PCI.225,226 Expanding the duration of DAPT up to 12 months should be considered in these patients. For patients undergoing fibrinolysis and subsequent PCI, DAPT is recommended for 12months. Clopidogrel is the P2Y12 inhibitor of choice as co-adjuvant and after fibrinolysis. Potent P2Y12 inhibitors have not been properly tested in patients undergoing fibrinolysis, and safety (i.e. bleeding complications) is not well established. However, in patients who underwent PCI after fibrinolysis, after a safety period (arbitrarily considered 48 h), there are no biological grounds to con- sider that potent P2Y12 inhibitors will add risk and not exert a benefit over clopidogrel as in the primary PCI setting. Whereas no dedicated study exists on optimal DAPT duration in patients at high bleeding risk, multiple studies have shown that short- ening DAPT to 6 months, compared with 12 months or longer, reduces the risk of major bleeding complications, with no apparent trade-off in ischaemic events.331,332 Two major studies have shown the benefit towards reduction of non-fatal ischaemic events in patients receiving longer than 12 months of DAPT.333,334 The DAPT Study included only roughly 10% of STEMI patients and no information has so far been provided with respect to the benefit of prolonging clopidogrel or prasugrel from 12 to 30 months in this patient subset. Hence, no formal recom- mendations are possible for the use of clopidogrel or prasugrel beyond 1 year.334 More recently, the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial examined two doses of ticagrelor (60 mg and 90mg b.i.d.) vs. placebo in patients with a history of MI 1–3 years previously and with high-risk features; the study showed a reduction in MACE with 90mg ticagrelor.333 There was no reduction in total mortality, but there was a borderline signal towards reduced cardio- vascular mortality (when both doses were pooled) consistent with the reduction in non-fatal outcomes.333 The 60mg (but not the 90 mg) ticagrelor (plus aspirin) regimen also significantly reduced the stroke risk compared with aspirin monotherapy. The ticagrelor regi- men was associated with a significantly increased bleeding risk. Patients with previous STEMI comprised more than 50% of the over- all PEGASUS-TIMI 54 population, and subgroup analysis has shown consistent results in patients with previous STEMI vs. NSTEMI.333 According to the available data, extension of DAPT beyond 1 year (up to 3 years) in the form of aspirin plus ticagrelor 60mg b.i.d. may be considered in patients who have tolerated DAPT without a bleed- ing complication and having one additional risk factor for ischaemic events. Gastric protection with a PPI is recommended for patients with a history of gastrointestinal bleeding and is appropriate for patients with multiple risk factors for bleeding, such as advanced age, concur- rent use of anticoagulants, steroids or non-steroidal anti-inflamma- tory drugs including high-dose aspirin, and Helicobacter pylori infection.335–337 Behavioural aspects after ST-elevation myocardial infarction Recommendations Classa Levelb It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.4,302,303,325–327 I A Participation in a cardiac rehabilitation programme is recommended.4,309,328 I A A smoking cessation protocol is indicated for each hospital participating in the care of STEMI patients. I C The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.4,322,323 IIb B STEMI = ST-segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. ESC Guidelines 31 Downloaded from by guest on 16 September 2017 32. ..... In the Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial (n = 15526, 50% STEMI), a low dose of rivaroxaban (2.5 mg twice daily), on top of aspirin plus clopidogrel, reduced the composite primary endpoint of cardiovas- cular death, MI, or stroke, but also all-cause mortality, over a mean follow-up of 13months.338 Stent thrombosis was reduced by one- third. However, this was associated with a three-fold increase in non- CABG-related major bleeding and intracranial haemorrhage.338 Based on the ATLAS ACS 2–TIMI 51 trial, in selected patients at low bleeding risk, the 2.5 mg dose of rivaroxaban may be considered in patients who receive aspirin and clopidogrel after STEMI. 7.3 Beta-blockers 7.3.1 Early intravenous beta-blocker administration In patients undergoing fibrinolysis, early i.v. beta-blocker treatment reduces the incidence of acute malignant ventricular arrhythmias, although there is no clear evidence of long-term clinical benefit.344–346 In patients undergoing primary PCI, the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial (n = 270) showed that the very early administration of i.v. metoprolol (15 mg) at the time of diagnosis in patients with anterior STEMI, no signs of heart failure, and SBP 120 mmHg was associated with a reduction in infarct size measured by CMR at 5–7 days (25.6 g vs. 32.0 g; P = 0.012), and higher LVEF at 6 months CMR (48.7% vs. 45.0%; P = 0.018) compared with control treatment.347,348 All patients without con- traindications received oral metoprolol within 24 h. The incidence of MACE (composite of death, admission as a result of heart failure, reinfarction, or malignant ventricular arrhythmias) at 2 years was 10.8% vs. 18.3% in the i.v. metoprolol and control arms (P = 0.065).348 Metoprolol treatment was associated with a significant reduction in the incidence and extent of MVO.349 The Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention (EARLY-BAMI) trial randomized 683 patients with STEMI within 12 h of onset to i.v. metoprolol (5 mg at recruitment and an additional 5 mg immediately before PCI) or placebo.350 All patients without contraindications Maintenance antithrombotic strategy after ST-elevation myocardial infarction Recommendations Classa Levelb Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.329 I A DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.186,187 I A A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleedingc .335–337 I B In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.5 I C In patients who are at high risk of severe bleeding complications, discontinuation of P2Y12 inhibitor therapy after 6 months should be considered.332,339,340 IIa B In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapyd should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).5 IIa C DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding. IIa C In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.341–343 IIa C In high ischaemic-risk patientse who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.333 IIb B In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered.338 IIb B The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation. III C AMI = acute myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LV = left ventricular; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. c History of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid user, and 2 or more of the following: age 65 years, dyspepsia, gastro-oesophageal reflux disease, H. pylori infection, and chronic alcohol use. d Oral anticoagulant, aspirin, and clopidogrel. e Defined as age 50 years, and at least one of the following additional high-risk features: age 65 years, diabetes mellitus on medication, a prior spontaneous AMI, multivessel CAD, or chronic renal dysfunction (eGFR 60 ml/min/1.73 m2). 32 ESC Guidelines Downloaded from by guest on 16 September 2017 33. ..... received oral metoprolol within 12 h. Early i.v. metoprolol admin- istration did not show any benefit in reducing CMR-based infarct size, the trial primary endpoint, available only in 342 patients (55%), or the level of cardiac biomarker release. Early i.v. metoprolol was associated with a borderline reduction of malig- nant ventricular arrhythmias (3.6% vs. 6.9%; P = 0.050). Patients treated with i.v. metoprolol showed no increased risk of haemo- dynamic instability, atrioventricular (AV) block, or MACE at 30 days. Post hoc analyses from primary PCI trials testing other hypotheses have suggested that early i.v. beta-blocker administration might be associated with a clinical benefit, but a selection bias cannot be excluded even after correction for imbal- ances in baseline characteristics.351,352 Based on the current avail- able evidence, early administration of i.v. beta-blockers at the time of presentation followed by oral beta-blockers should be considered in haemodynamically stable patients undergoing primary PCI. 7.3.2 Mid- and long-term beta-blocker treatment The benefit of long-term treatment with oral beta-blockers after STEMI is well established, although most of the supporting data come from trials performed in the pre-reperfusion era.353 A recent multicentre registry enrolling 7057 consecutive patients with AMI showed a benefit in terms of mortality reduction at a median follow-up of 2.1 years associated with beta-blocker pre- scription at discharge, although no relationship between dose and outcomes could be identified.354 Using registry data, the impact of newly introduced beta-blocker treatment on cardiovascular events in 19 843 patients with either ACS or undergoing PCI was studied.355 At an average of 3.7 years of follow-up, the use of beta- blockers was associated with a significant mortality reduction (adjusted HR 0.90, 95% CI 0.84–0.96). The association between beta-blockers and outcomes differed significantly between patients with and without a recent MI (HR for death 0.85 vs. 1.02; Pint = 0.007). Opposing these results, in a longitudinal observatio- nal propensity-matched study including 6758 patients with pre- vious MI, beta-blocker use was not associated with a lower risk of cardiovascular events or mortality.356 Based on the current evi- dence, routine administration of beta-blockers in all post-STEMI patients should be considered as discussed in detail in the heart failure guidelines;6 beta-blockers are recommended in patients with reduced systolic LV function (LVEF _40%), in the absence of contraindications such as acute heart failure, haemodynamic insta- bility, or higher degree AV block. Agents and doses of proven effi- cacy should be administered.357–361 As no study has properly addressed beta-blocker duration to date, no recommendation in this respect can be made. Regarding the timing of initiation of oral beta-blocker treatment in patients not receiving early i.v. beta- blockade, a retrospective registry analysis on 5259 patients sug- gested that early (i.e. 24 h) beta-blocker administration con- veyed a survival benefit compared with a delayed one.362 Therefore, in haemodynamically stable patients, oral beta-blocker initiation should be considered within the first 24 h. 7.4 Lipid-lowering therapy The benefits of statins in secondary prevention have been unequivocally demonstrated,363 and trials have shown the benefits of early and intensive statin therapy in ACS.364,365 A meta-analysis of trials comparing more- vs. less-intensive LDL-C lowering with statins indicated that more-intensive statin therapy produced greater reductions in the risks of cardiovascular death, non-fatal MI, ischaemic stroke, and coronary revascularization.366 For every 1.0 mmol/L reduction in LDL-C, these further reductions in risk were similar to the proportional reductions in the trials of statins vs. control. Therefore, statins are recommended in all patients with AMI, irrespective of cholesterol concentration at presenta- tion. Lipid-lowering treatment should be started as early as possi- ble, as this increases patient adherence after discharge, and given as high-intensity treatment, as this is associated with early and sus- tained clinical benefits.4 The intensity of statin therapy should be increased in those receiving a low- or moderate-intensity statin treatment at presentation, unless they have a history of intoler- ance to high-intensity statin therapy or other characteristics that may influence safety.366–368 The treatment goal is an LDL-C con- centration of 1.8 mmol/L (70 mg/dL) or at least 50% reduction in LDL-C if the baseline LDL-C level is 1.8–3.5 mmol/L.4,367,369 The use of lower-intensity statin therapy should be considered in patients at increased risk of side effects from statins (e.g. elderly, hepatic or renal impairment, previous side effects, or a potential for interaction with essential concomitant therapy). Following MI, the lipid profile goes through phasic changes, with small reduc- tions in total cholesterol, LDL-C, and HDL-C, and increases in tri- glycerides within the first 24 h.370,371 A lipid profile should be obtained as early as possible after admission for STEMI and can be non-fasting, as total and HDL-C show little diurnal variation and LDL-C variation is within 10%.372 Lipids should be re-evaluated 4–6 weeks after the ACS to determine whether the target levels have been reached and regarding safety issues; the lipid lowering therapy can then be adjusted accordingly. Trial results with high doses of atorvastatin and simvastatin366,373–375 favour a high- intensity statin. In patients known to be intolerant of any dose of statin, treat- ment with ezetimibe should be considered. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18 144 patients with a recent ACS (29% with STEMI) were randomized to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg alone (simvastatin was up-titrated to 80 mg if LDL-C was 79 mg/dL or 2.04 mmol/L).376 Over a period of 7 years, the composite primary endpoint of cardiovascular death, MI, hospital admission for unstable angina, coronary revas- cularization, or stroke was significantly lower in the combined treatment arm compared with the statin-only arm (32.7% vs. 34.7%; HR 0.94, 95% CI 0.89–0.99). Recent data from phase I–III trials show that proprotein con- vertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease LDL- C up to 60%, either as monotherapy or in addition to a statin dose, and also have beneficial effects on triglycerides and HDL- C.377–380 Meta-analyses of existing trials with more than 10 000 patients indicate a significant mortality benefit (HR 0.45, 95% CI 0.23–0.86) but are based on relatively few endpoints.378,381 In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial consist- ing of 27 564 patients with atherosclerotic cardiovascular disease, additional risk factors, and LDL 70 mg/dL (1.8 mmol/L), who ESC Guidelines 33 Downloaded from by guest on 16 September 2017 34. .....were already receiving moderate or high intensity statin therapy as compared to placebo, evolocumab injections reduced the pri- mary composite endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 15% in relative rate and by 1.5% in absolute rate. There were no differences in all-cause mortality or cardiovascular mortality and no significant differences in adverse events.382 Given the moderate effect over 2 years and the absence of mortality reduc- tion, its use should still be restricted to selected high-risk patients. Based on this relatively limited body of evidence, clinicians should consider adding a non-statin treatment to patients at high risk who do not reach treatment targets after STEMI despite the maximum tolerated dose of statin. 7.5 Nitrates The routine use of nitrates in STEMI was of no benefit in a randomized controlled trial against placebo and is therefore not recommended.383 Intravenous nitrates may be useful during the acute phase in patients with hypertension or heart failure, pro- vided there is no hypotension, RV infarction, or use of phospho- diesterase type 5 inhibitors in the previous 48 h. Following the acute phase, nitrates remain valuable agents to control residual angina symptoms. 7.6 Calcium antagonists A meta-analysis of 17 trials involving calcium antagonists early in the course of STEMI showed no beneficial effect on death or rein- farction, with a trend of higher mortality for patients treated with nifedipine. Therefore, routine use of calcium antagonists in the acute phase is not indicated.384,385 In the chronic phase, a random- ized controlled trial allocating 1775 patients with MI not on beta- blockers to verapamil or placebo found that the risk of mortality and reinfarction was reduced with verapamil.386 Thus, in patients with contraindications to beta-blockers, particularly in the pres- ence of obstructive airway disease, calcium antagonists are a rea- sonable option for patients without heart failure or impaired LV function. Routine use of dihydropyridines, on the other hand, has failed to show benefit after STEMI,387 and they should therefore only be prescribed for clear additional indications such as hyper- tension or residual angina.388 7.7 Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers ACE inhibitors are recommended in patients with an impaired LVEF (_40%) or who have experienced heart failure in the early phase.383,389–392 A systematic overview of trials of ACE inhibition early in STEMI indicated that this therapy is safe, well tolerated, and associated with a small but significant reduction in 30-day mortality, with most of the benefit observed in the first week.383,393 Treatment with ACE inhibitors is recommended in patients with systolic LV dysfunction or heart failure, hyperten- sion, or diabetes, and should be considered in all STEMI patients.394,395 Patients who do not tolerate an ACE inhibitor should be given an angiotensin II receptor blocker (ARB). In the context of STEMI, valsartan was found to be non-inferior to cap- topril in the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial.396 7.8 Mineralocorticoid/aldosterone receptor antagonists Mineralocorticoid receptor antagonist (MRA) therapy is recom- mended in patients with LV dysfunction (LVEF _40%) and heart failure after STEMI.397–400 Eplerenone, a selective aldosterone receptor antagonist, has been shown to reduce morbidity and mortality in these patients. The Eplerenone Post-AMI Heart fail- ure Efficacy and SUrvival Study (EPHESUS) randomized 6642 post-MI patients with LV dysfunction (LVEF _40%) and symptoms of heart failure/diabetes to eplerenone or placebo within 3–14 days after their infarction.397 After a mean follow-up of 16 months, there was a 15% relative reduction in total mortality and a 13% reduction in the composite of death and hospitalization for cardi- ovascular events. Two recent studies have indicated a beneficial effect of early treatment with MRA in the setting of STEMI without heart failure. The Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction (REMINDER) trial randomized 1012 patients with acute STEMI without heart failure to eplerenone or placebo within 24 h of symptom onset.401 After 10.5 months, the primary combined end- point [CV mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of heart failure, sustained ventricular tachy- cardia or fibrillation, ejection fraction _40%, or elevated B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic pep- tide (NT-proBNP)] occurred in 29.4% of the active group vs. 18.2% in the placebo group (P 0.0001), with the difference pri- marily driven by BNP levels.401 The Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) trial randomized 1603 patients with acute STEMI or high-risk NSTEMI to a single i.v. bolus of potassium canrenoate (200 mg) followed by spironolactone (25 mg daily) vs. placebo. Overall, the study found no effect on the composite out- come (death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening heart failure) at 6 months. In an exploratory analysis of the STEMI subgroup (n = 1229), the outcome was significantly reduced in the active treatment group (HR 0.20, 95% CI 0.06–0.70).402 Future studies will clarify the role of MRA treat- ment in this setting. 34 ESC Guidelines Downloaded from by guest on 16 September 2017 35. ..... When using MRA, care should be taken with reduced renal func- tion [creatinine concentration 221 mmol/L (2.5 mg/dL) in men and 177 mmol/L (2.0 mg/dL) in women] and routine monitoring of serum potassium is warranted. Figures 5 and 6 present the mostly prescribed interventions (class I and IIa) in patients undergoing primary PCI or fibrinolysis strategies. 8. Complications following ST- segment elevation myocardial infarction Expanded information about complications following STEMI is pre- sented in the Web Addenda. Routine therapies in the acute, subacute, and long-term phases: beta-blockers, angiotensin-converting enzyme inhibi- tors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and lipid-lowering treatments after ST- elevation myocardial infarction Recommendations Classa Levelb Beta-blockers Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF _40% unless contraindicated.357–361 I A Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without con- traindications, with no signs of acute heart failure, and with an SBP 120 mmHg.346–348,350,403 IIa A Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.344,354–356,404,405 IIa B Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia.344 III B Lipid lowering therapies It is recommended to start high-intensity statin therapyc as early as possible, unless contraindicated, and maintain it long- term.364,366,368 I A An LDL-C goal of 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.367,369,376,382 I B It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation.369,406 I C In patients with LDL-C 1.8 mmol/L (70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered.376,382 IIa A ACE inhibitors/ARBs ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct.383 I A An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.396,407 I B ACE inhibitors should be considered in all patients in the absence of contraindications.394,395 IIa A MRAs MRAs are recommended in patients with an LVEF _40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia.397 I B AV = atrioventricular; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-seg- ment elevation myocardial infarction. a Class of recommendation. b Level of evidence. c High-intensity statin defined as atorvastatin 40–80 mg and rosuvastatin 20–40 mg. ESC Guidelines 35 Downloaded from by guest on 16 September 2017 36. Figure 5 "Do not forget" interventions in STEMI patients undergoing a primary PCI strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; ED = emergency department; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percuta- neous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin. Mostly prescribed interventions (class I, green, and IIa, yellow) are presented along with the expected timing of delivery. Solid lines represent recur- rent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered. 1 Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous (in patients not already on an aspirin maintenance dose). 2 Prasugrel loading dose: 60 mg. Ticagrelor loading dose: 180 mg. If there are contra-indications for prasugrel/ticagrelor or these are not available, a loading dose of clopidogrel (600 mg) is indicated. 3 If the interventional cardiologist is not expert in radial access, the femoral route is then preferred. 4 Enoxaparin or bivalirudin are alternatives to unfractionated heparin (Class IIa A). 5 Aspirin maintenance dose: 75–100 mg oral. 6 Prasugrel maintenance dose: 10 mg once daily. Ticagrelor maintenance dose: 90 mg twice daily. If there are contra-indications for pra- sugrel/ticagrelor or these are not available, clopidogrel maintenance (75 mg daily) is indicated. a 90 min represents the maximum target time to PCI-mediated reperfusion. For patients presenting in a PCI-centre, this target time is 60 min. b Prolongation of ticagrelor (60 mg twice daily) in addition to aspirin may be considered for up to 36 months in patients at high ischaemic risk who have tolerated DAPT without a bleeding complication. 36 ESC Guidelines Downloaded from by guest on 16 September 2017 37. Figure 6 "Do not forget" interventions in STEMI patients undergoing a successful fibrinolysis strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin. Mostly prescribed interventions (class I, green, and IIa, light yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered. 1 Enoxaparin dose: 30 mg i.v. bolus followed by 1 mg/kg subcutaneous every 12 hours (dose adjustment for 75 years and renal insuffi- ciency is presented in Table 9). Unfractionated heparin is an alternative to enoxaparin. 2 Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous. 3 Clopidogrel loading dose: 300 mg oral (75 mg in 75 years). 4 Aspirin maintenance dose: 75–100 mg oral 5 Clopidogrel maintenance therapy: 75 mg daily. 6 48 hours after fibrinolysis, switch to prasugrel/ticagrelor may be considered in PCI-treated patients. ESC Guidelines 37 Downloaded from by guest on 16 September 2017 38. ..... 8.1 Myocardial dysfunction 8.1.1 Left ventricular dysfunction See Web Addenda. 8.1.2 Right ventricular involvement See Web Addenda. 8.2 Heart failure 8.2.1 Clinical presentations See Web Addenda. 8.2.2 Management Patients with heart failure should be under continuous monitoring of heart rhythm, blood pressure, and urinary output. The mecha- nism of heart failure should be assessed early by physical examina- tion, ECG, echocardiography, and (when not rapidly controlled) with invasive haemodynamic monitoring, and corrected as soon as possible. Patients with pulmonary congestion and SaO2 90% or partial pressure of oxygen (PaO2) 60 mmHg (8.0 kPa) require oxygen therapy and SaO2 monitoring to correct hypoxaemia, with a tar- get of 95%, and may require periodic blood-gas assessment. Initial pharmacological treatment includes i.v. loop diuretics (e.g. furose- mide 20–40 mg i.v. with repeated doses at intervals as needed according to clinical evolution and diuresis) and, if blood pressure allows it, i.v. nitrates, avoiding hypotension or excessive falls in blood pressure. The early use of beta-blockers, ACE inhibitors/ ARBs, and MRA is recommended in the absence of hypotension, hypovolaemia, or renal dysfunction. Causal treatment is essential. Coronary revascularization should be performed early when sig- nificant CAD is still present. Rhythm disturbances, valvular dys- function, and hypertension should be corrected as soon as possible. Hypertension should be treated promptly with oral ACE inhibitors/ARBs and i.v. nitrates. In very severe cases, sodium nitroprusside infusion may be necessary. Persistent myocardial ischaemia should be treated with early coronary revascularization. Atrial and ventricular dysrhythmias, and valvular dysfunction or Recommendations for the management of left ventricular dysfunction and acute heart failure in ST-elevation myocar- dial infarction Recommendations Classa Levelb ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF _40% and/or heart failure to reduce the risk of hospitalization and death.390,396,412,413 I A Beta-blocker therapy is recommended in patients with LVEF _40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.358–361,414–416 I A An MRA is recommended in patients with heart failure and LVEF _40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.397 I B Loop diuretics are recommended in patients with acute heart failure with symptoms/signs of fluid overload to improve symptoms. I C Nitrates are recommended in patients with symptomatic heart failure with SBP 90 mmHg to improve symptoms and reduce congestion. I C Oxygen is indicated in patients with pulmonary oedema with SaO2 90% to maintain a saturation 95%. I C Patient intubation is indicated in patients with respiratory failure or exhaustion, leading to hypoxaemia, hypercapnia, or acidosis, and if non-invasive ventilation is not tolerated. I C Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) should be considered in patients with respiratory distress (respiratory rate 25 breaths/min, SaO2 90%) without hypotension.410,411,417–419 IIa B Intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated SBP to control blood pressure and improve symptoms. IIa C Opiates may be considered to relieve dyspnoea and anxiety in patients with pulmonary oedema and severe dyspnoea. Respiration should be monitored.6,408 IIb B Inotropic agents may be considered in patients with severe heart failure with hypotension refractory to standard medical treatment. IIb C ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SaO2 = arterial oxygen saturation; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction. a Class of recommendation. b Level of evidence. 38 ESC Guidelines Downloaded from by guest on 16 September 2017 39. ..... mechanical complications, should be treated as appropriate (see specific sections in this document). Severely symptomatic patients with pulmonary congestion may also need i.v. morphine to reduce dyspnoea and anxiety, but rou- tine use is not recommended due to concerns about its safety, as it may induce nausea and hypopnea.408,409 Non-invasive positive pressure ventilation (continuous positive airway pressure, bipha- sic positive airway pressure) or high-flow nasal cannula is effective in treating pulmonary oedema and should be considered in patients with respiratory distress (respiratory rate 25 breaths/ min, SaO2 90%) and started soon.410,411 Endotracheal intubation and ventilatory support may be required in patients unable to achieve adequate oxygenation, or in those with excess respiratory work or evidence of hypercapnia due to respiratory exhaustion. Ultrafiltration to reduce fluid overload may be considered in patients who are refractory to diuretics, especially in patients with hyponatraemia. In patients with heart failure and adequate blood pressure (SBP 90mmHg), but a severe reduction in cardiac output resulting in compromised vital organ perfusion not responding to standard therapy, treatment with dobutamine or levosimendan may be considered. However, the clinical evidence of levosimendan in cardiogenic shock is limited. Further details on the management of acute heart failure can be found in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.6 8.2.2.1 Management of hypotension In patients with hypotension and normal perfusion without evidence of congestion or volume overload (i.e. collapsible inferior vena cava), gentle volume loading should be attempted after ruling out complica- tions such as mechanical or severe mitral regurgitation, with central pressure monitoring. Bradycardia or tachyarrhythmias should be cor- rected or controlled. In patients with RV infarction, volume overload- ing should be avoided because it might worsen haemodynamics.420 If hypotension persists, inotropic therapy, preferably with dobut- amine, may be considered.420 8.2.2.2 Management of cardiogenic shock Cardiogenic shock is defined as persistent hypotension (SBP 90mmHg) despite adequate filling status with signs of hypoperfu- sion. It complicates 6–10% of all STEMI cases and remains a leading cause of death, with in-hospital mortality rates 50%.421 Shock is also considered to be present if i.v. inotropes and/or mechanical support are needed to maintain an SBP 90mmHg. In STEMI patients present- ing with cardiogenic shock in which PCI-mediated reperfusion is esti- mated to occur 120min, immediate fibrinolysis and transfer to a PCI centre should be considered. In these cases, upon arrival at the PCI centre, emergent angiography is indicated, regardless of the ST resolution and the time from fibrinolysis administration. It is usually associ

therapies for pre- and afterload reduction, there is limited evidence for the system- atic use of inotropic and vasopressor agents as well as mechanical support. Similarly, the benefit of routine complete revascularization during the index PCI procedure has not been formally demonstrated. The use of IABP has not met prior expectations of benefit, while LV assist devices and ECMO are increasingly popular but have not been sufficiently evaluated in clinical trials. Systematic evaluation of phar- macological and interventional strategies and LV assist devices for patients with shock are urgently needed. Myocardial repair/rescue The effectiveness and safety of novel therapies able to replace dead myocardium or prevent poor remodelling (e.g. cell therapy or gene therapy) is an unfulfilled promise. There is a strong need for basic research studies to better understand the biological processes involved in cardiac development and repair, in order for there to be strong grounds to translate studies into clinically relevant animal models and finally into humans. Need for observational data and real- world evidence In order to understand shortcomings and challenges in clinical prac- tice, for quality assessment and for benchmarking, unselected and validated registries and clinical databases are needed. In this docu- ment, we have specified quality indicators intended to measure and compare the quality of health service provision and serve as a founda- tion for quality improvement initiatives. Their effects on procedural and clinical outcomes need to be evaluated. 46 ESC Guidelines Downloaded from by guest on 16 September 2017 47. ..... Need for pragmatic real-life clinical trials One major limitation of highly selective controlled clinical trials is their applicability in the real world. Strict inclusion criteria, tailored management, and very close follow-up results in a bias that precludes universal implementation. An opportunity is the implementation of pragmatic clinical trials including registry-based randomized clinical trials.477 These trials are less selective and less expensive alternatives to classical ones, especially for therapies used in clinical practice. 12. Key messages (1) Epidemiology of STEMI: Although the rate of mortality associated with ischaemic heart disease have reduced in Europe over the last few decades, this is still the single most common cause of death worldwide. The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively. Despite the decline in acute and long-term death associated with STEMI, in parallel with the widespread use of reperfusion, mortality remains substantial. The in-hospital mortality rates of unselected patients with STEMI in national European registries vary between 4–12%. (2) Gender aspects: Women tend to receive reperfusion therapy and other evidence-based treatments less frequently and/or in a delayed way than men. It is important to highlight that women and men receive equal benefit from a reperfusion and other STEMI- related therapies, and so both genders must be managed equally. (3) ECG and STEMI diagnosis: In some cases, patients may have coro- nary artery occlusion/global ischaemia in the absence of character- istic ST elevation (e.g. bundle branch block, ventricular pacing, hyperacute T-waves, isolated ST-depression in anterior leads, and/ or universal ST depression with ST-elevation in aVR). In patients with the mentioned ECG changes and clinical presentation com- patible with ongoing myocardial ischaemia, a primary PCI strategy (i.e. urgent angiography and PCI if indicated) should be followed. (4) Reperfusion strategy selection: STEMI diagnosis (defined as the time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent) is the time zero in the reperfusion strategy clock. STEMI patients should undergo a primary PCI strategy unless the anticipated abso- lute time from STEMI diagnosis to PCI-mediated reperfusion is 120 min, when fibrinolysis should be initiated immediately (i.e. within 10min of STEMI diagnosis). (5) STEMI management networks: Coordination between EMS and hospitals with common written protocols is at the centre of STEMI management. EMS should transfer patients to 24/7 high- volume PCI centres irrespective of whether the primary treatment strategy is PCI or pre-hospital fibrinolysis. EMS should always alert the PCI centre immediately after selection of the reperfusion strat- egy. Patient transfer to the PCI centre should bypass the emer- gency department. (6) Cardiac arrest and reperfusion strategy: Patients with ST-elevation on post-resuscitation ECG should undergo a primary PCI strategy. In cases without ST-segment elevation on post-resuscitation ECG but with a high suspicion of ongoing myocardial ischaemia, urgent angiography should be done within 2 h after a quick evaluation to exclude non-coronary causes. In all cases, the decision to perform urgent coronary angiography should take into account factors associated with poor neurological outcome. (7) Technical aspects during primary PCI: Routine radial access and routine DES implant is the standard of care during primary PCI. Routine thrombus aspiration or deferred stenting are contraindicated. (8) Management of non-IRA lesions: Treatment of severe stenosis (evaluated either by angiography or FFR) should be considered before hospital discharge (either immediately during the index PCI or staged at a later time). In cardiogenic shock, non-IRA PCI should be considered during the index procedure. (9) Antithrombotic therapy: Anticoagulants and DAPT are the cor- nerstone of the pharmacological approach in the acute phase of STEMI. Primary PCI: unfractionated heparin (enoxaparin and biva- lirudin may be alternative), and loading dose of aspirin and prasu- grel/ticagrelor. Fibrinolysis: enoxaparin (unfractionated heparin may be alternative), and loading dose of aspirin and clopidogrel. Maintenance therapy in the majority of patients is based on one year DAPT in the form of aspirin plus prasugrel/ticagrelor. (10) Early care: After reperfusion therapy, patients should be moni- tored for at least 24h. Early ambulation and early discharge are the best option in uncomplicated patients. Consequently, time for implementing secondary prevention is limited highlighting the importance of close collaboration between all stakeholders. (11) Special patient subsets: Patients taking oral anticoagulants with renal insufficiency and/or the elderly represent a challenge in terms of optimal antithrombotic therapy. Special attention should be paid to dose adjustment of some pharmacological strategies in these subsets. Patients with diabetes and those not undergoing reperfusion represent another subset of patients that require addi- tional attention. (12) Imaging in STEMI: Non-invasive imaging is very important for the acute and long-term management of STEMI patients. (13) MINOCA: A sizeable proportion of STEMI patients do not present significant coronary artery stenosis on urgent angiography. It is important to perform additional diagnostic tests in these patients to identify the aetiology and tailor appropriate therapy, which may be different from typical STEMI. (14) Quality indicators: In some cases, there is a gap between optimal guideline-based treatment and actual care of STEMI patients. In order to reduce this gap, it is important to measure established quality indicators to audit practice and improve outcomes in real- life. The use of well-defined and validated quality indicators to measure and improve STEMI care is recommended. ESC Guidelines 47 Downloaded from by guest on 16 September 2017 48. 13. Evidenced-based ‘to do and not to do’ messages from the Guidelines Recommendations Recommendations for initial diagnosis Classa Levelb Twelve-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min. I B ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI. I B Recommendations for relief of hypoxaemia and symptoms Routine oxygen is not recommended in patients with SaO2 90%. III B Recommendations for cardiac arrest A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI. I B Targeted temperature management is indicated early after resuscitation of cardiac arrest patients who remain unresponsive. I B Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended. III B Recommendations for logistics of pre-hospital care It is recommended that the pre-hospital management of STEMI patients is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible. I B It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay. I B It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory. I B Recommendations for reperfusion therapy Reperfusion therapy is indicated in all patients with symptoms of ischaemia of _ 12 h duration and persistent ST-segment elevation. I A If primary PCI cannot be performed in a timely way after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications. I A In asymptomatic patients, routine PCI of an occluded IRA 48 h after onset of STEMI is not indicated. III A Recommendations for procedural aspects of the primary PCI strategy Primary PCI of the IRA is indicated. I A Stenting is recommended (over balloon angioplasty) for primary PCI. I A Stenting with new-generation DES is recommended over BMS for primary PCI. I A Radial access is recommended over femoral access if performed by an experienced radial operator. I A Routine use of thrombus aspiration is not recommended. III A Routine use of deferred stenting is not recommended. III B Recommendations for periprocedural and post-procedural antithrombotic therapy in patients undergoing primary PCI A potent P2Y12 inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recom- mended before (or at latest at the time of) PCI and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. I A Continued 48 ESC Guidelines Downloaded from by guest on 16 September 2017 49. Aspirin oral or i.v. (if unable to swallow) is recommended as soon as possible for all patients without contraindications. I B Fondaparinux is not recommended for primary PCI. III B Recommendations for Fibrinolytic therapy When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diag- nosis, preferably in the pre-hospital setting. I A A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended. I B Oral or i.v. aspirin is indicated. I B Clopidogrel is indicated in addition to aspirin. I A Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hos- pital stay up to 8 days. The anticoagulant can be: I A Enoxaparin i.v. followed by s.c. (preferred over UFH). I A UFH given as a weight-adjusted i.v. bolus followed by infusion. I B Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis. I A Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock. I A Rescue PCI is indicated immediately when fibrinolysis has failed (50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia. I A Angiography and PCI of the IRA, if indicated, is recommended between 2–24 h after successful fibrinolysis. I A Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis. I B Recommendations for imaging and stress testing in STEMI patients Routine echocardiography during hospital stay to assess resting LV and RV function, detect early post-MI mechanical complica- tions, and exclude LV thrombus is recommended in all patients. I B Recommendations for behavioural aspects after STEMI It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination. I A Participation in a cardiac rehabilitation programme is recommended. I A Recommendations for maintenance antithrombotic strategy after STEMI Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated. I A DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contra- indicated) is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding. I A A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding. I B Recommendations for routine therapies in the acute, subacute, and long-term phases Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF _40% unless contraindicated. I A Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure, or AV block or severe bradycardia. III B It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term. I A An LDL-C goal of 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended. I B ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct. I A Continued ESC Guidelines 49 Downloaded from by guest on 16 September 2017 50. ..... 14. Web addenda All Web figures and Web tables are available in the online Web Addenda at: European Heart Journal online and also via the ESC Website at: Guidelines/Acute-Myocardial-Infarction-in-patients-presenting-with- ST-segment-elevation-Ma 15. Appendix ESC Committee for Practice Guidelines (CPG): Stephan Windecker (Chairperson) (Switzerland), Victor Aboyans (France), Stefan Agewall (Norway), Emanuele Barbato (Italy), He´ctor Bueno (Spain), Antonio Coca (Spain), Jean-Philippe Collet (France), Ioan Mircea Coman (Romania), Veronica Dean (France), Victoria Delgado (The Netherlands), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Gerhard Hindricks (Germany), Bernard Iung (France), Peter Ju¨ni (Canada), Hugo A. Katus (Germany), Juhani Knuuti (Finland), Patrizio Lancellotti (Belgium), Christophe Leclercq (France), Theresa McDonagh (UK), Massimo Francesco Piepoli (Italy), Piotr Ponikowski (Poland), Dimitrios J. Richter (Greece), Marco Roffi (Switzerland), Evgeny Shlyakhto (Russia), Iain A. Simpson (UK), Jose Luis Zamorano (Spain). ESC National Cardiac Societies actively involved in the review process of the 2017 ESC Guidelines for the manage- ment of acute myocardial infarction in patients presenting with ST-segment elevation: Algeria: Algerian Society of Cardiology, Mohamed Chettibi; Armenia: Armenian Cardiologists Association, Hamlet G. Hayrapetyan; Austria: Austrian Society of Cardiology, Bernhard Metzler; Azerbaijan: Azerbaijan Society of Cardiology, Firdovsi An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors. I B MRAs are recommended in patients with an ejection fraction _40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia. I B Recommendations for the management of LV dysfunction and acute heart failure in STEMI ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF _40% and/or heart failure to reduce the risk of hospitalization and death. I A Beta-blocker therapy is recommended in patients with LVEF _40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure. I A An MRA is recommended in patients with heart failure and LVEF _40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death. I B Recommendations for the management of cardiogenic shock in STEMI Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suit- able for PCI, or PCI has failed, emergency CABG is recommended. I B Routine intra-aortic balloon pumping is not indicated. III B Recommendations for management of atrial fibrillation Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control. III A Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm. III B Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated. III B Recommendations for management of ventricular arrhythmias and conduction disturbances in the acute phase Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated. I B Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful. III B Recommendations for long-term management of ventricular arrhythmias and risk evaluation for sudden death ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (New York Heart Association class II–III) and LVEF _35%, despite optimal medical therapy for 3 months and at least 6 weeks after MI, who are expected to survive for at least 1 year with good functional status. I A Recommendations with a class I or III and a level of evidence A or B. See ‘Abbreviations and acronyms’ list for explanation of abbreviations. a Class of recommendation. b Level of evidence. 50 ESC Guidelines Downloaded from by guest on 16 September 2017 51. ..... Ibrahimov; Belarus: Belorussian Scientific Society of Cardiologists, Volha Sujayeva; Belgium: Belgian Society of Cardiology, Christophe Beauloye; Bosnia and Herzegovina: Association of Cardiologists of Bosnia and Herzegovina, Larisa Dizdarevic-Hudic; Bulgaria: Bulgarian Society of Cardiology, Kiril Karamfiloff; Croatia: Croatian Cardiac Society, Bosko Skoric; Cyprus: Cyprus Society of Cardiology, Loizos Antoniades; Czech Republic: Czech Society of Cardiology, Petr Tousek; Denmark: Danish Society of Cardiology, Christian Juhl Terkelsen; Egypt: Egyptian Society of Cardiology, Sameh Mohamad Shaheen; Estonia: Estonian Society of Cardiology, Toomas Marandi; Finland: Finnish Cardiac Society, Matti Niemel€a; The Former Yugoslav Republic of Macedonia: Macedonian Society of Cardiology, Sasko Kedev; France: French Society of Cardiology, Martine Gilard; Georgia: Georgian Society of Cardiology, Alexander Aladashvili; Germany: German Cardiac Society, Albrecht Elsaesser; Greece: Hellenic Society of Cardiology, Ioannis Georgios Kanakakis; Hungary: Hungarian Society of Cardiology, Be´la Merkely; Iceland: Icelandic Society of Cardiology, Thorarinn Gudnason; Israel: Israel Heart Society, Zaza Iakobishvili; Italy: Italian Federation of Cardiology, Leonardo Bolognese; Kazakhstan: Association of Cardiologists of Kazakhstan, Salim Berkinbayev; Kosovo: Kosovo Society of Cardiology, Gani Bajraktari; Kyrgyzstan: Kyrgyz Society of Cardiology, Ilja Zake; Libya: Libyan Cardiac Society, Hisham Ben Lamin; Lithuania: Lithuanian Society of Cardiology, Olivija Gustiene; Luxembourg: Luxembourg Society of Cardiology, Bruno Pereira; Malta: Maltese Cardiac Society, Robert G. Xuereb; Morocco: Moroccan Society of Cardiology, Samir Ztot; Norway: Norwegian Society of Cardiology, Vibeke Juliebø; Poland: Polish Cardiac Society, Jacek Legutko; Portugal: Portuguese Society of Cardiology, Ana Teresa Timoteo; Romania: Romanian Society of Cardiology, Gabriel Tatu-Chit¸oiu; Russian Federation: Russian Society of Cardiology, Alexey Yakovlev; San Marino: San Marino Society of Cardiology, Luca Bertelli; Serbia: Cardiology Society of Serbia, Milan Nedeljkovic; Slovakia: Slovak Society of Cardiology, Martin Studencan; Slovenia: Slovenian Society of Cardiology, Matjaz Bunc; Spain: Spanish Society of Cardiology, Ana Maria Garcıa de Castro; Sweden: Swedish Society of Cardiology, Petur Petursson; Switzerland: Swiss Society of Cardiology, Raban Jeger; Tunisia: Tunisian Society of Cardiology and Cardio-Vascular Surgery, Mohamed Sami Mourali; Turkey: Turkish Society of Cardiology, Aylin Yildirir; Ukraine: Ukrainian Association of Cardiology, Alexander Parkhomenko; United Kingdom: British Cardiovascular Society, Chris P. 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